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(54) Title: **METHODS FOR USING JNK INHIBITORS FOR TREATING OR PREVENTING DISEASE-RELATED WASTING**

(57) Abstract: The present invention relates to methods useful for the treatment or prevention of disease-related wasting. The methods of the invention comprise the administration of an effective amount of a JNK Inhibitor. In one embodiment, the disease is HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease or tuberculosis. The methods can further comprise the administration of a therapeutic or prophylactic agent useful for the treatment or prevention of HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease, chronic infectious diseases (e.g., osteoarthritis and bacterial endocarditis), chronic inflammatory diseases (e.g., scleroderma and mixed connective tissue disease) or tuberculosis.

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**METHODS FOR USING JNK INHIBITORS FOR  
TREATING OR PREVENTING DISEASE-RELATED WASTING**

This application claims the benefit of U.S. provisional application no. 60/383,202, filed May 24, 2003, the contents of which are incorporated by reference herein in their entirety.

1. **FIELD OF INVENTION**

The present invention relates to methods useful for treating or preventing disease-related wasting in a patient, comprising administering an effective amount of a JNK Inhibitor to a patient in need thereof.

15 2. **BACKGROUND OF THE INVENTION**

2.1 **JUN N-TERMINAL KINASE (JNK)**

The Jun N-terminal kinase (JNK) pathway is activated by exposure of cells to environmental stress or by treatment of cells with pro-inflammatory cytokines. Targets of the JNK pathway include the transcription factors c-jun and ATF2 (Whitmarsh A.J., and Davis R.J. *J. Mol. Med.* 74:589-607, 1996). These transcription factors are members of the basic leucine zipper (bZIP) group that bind as homo- and hetero-dimeric complexes to AP-1 and AP-1-like sites in the promoters of many genes (Karin M., Liu Z.G. and Zandi E. *Curr. Opin. Cell Biol.* 9:240-246, 1997). JNK binds to the N-terminal region of c-jun and ATF-2 and phosphorylates two sites within the activation domain of each transcription factor (Hibi M., Lin A., Smeal T., Minden A., Karin M. *Genes Dev.* 7:2135-2148, 1993; Mohit A.A., Martin M.H., and Miller C.A. *Neuron* 14:67-75, 1995). Three JNK enzymes have been identified as products of distinct genes (Hibi et al, *supra*; Mohit et al., *supra*). Ten different isoforms of JNK have been identified. These represent alternatively spliced forms of three different genes: JNK1, JNK2 and JNK3. JNK1 and 2 are ubiquitously expressed in human tissues, whereas JNK3 is selectively expressed in the brain, heart and testis (Dong C., Yang D., Wysk M., Whitmarsh A., Davis R., Flavell R. *Science* 270:1-4, 1998). Gene transcripts are alternatively spliced to produce four-JNK1 isoforms, four-JNK2 isoforms and two-JNK3 isoforms. JNK1 and 2 are expressed widely in mammalian tissues, whereas JNK3 is expressed almost exclusively in the brain. Selectivity of JNK signaling is achieved via

5 specific interactions of JNK pathway components and by use of scaffold proteins that selectively bind multiple components of the signaling cascade. JIP-1 (JNK-interacting protein-1) selectively binds the MAPK module, MLK 6 JNKK2 6 JNK. JIP-1 has no binding affinity for a variety of other MAPK cascade enzymes. Different scaffold proteins are likely to exist for other MAPK signaling cascades to preserve substrate specificity.

10 JNKs are activated by dual phosphorylation on Thr-183 and Tyr-185. JNKK1 (also known as MKK 4) and JNKK2 (MKK7), two MAPKK level enzymes, can mediate JNK activation in cells (Lin A., Minden A., Martinetto H., Claret F.-Z., Lange-Carter C., Mercurio F., Johnson G.L., and Karin M. *Science* 268:286-289, 1995; Tournier C., Whitmarsh A.J., Cavanagh J., Barrett T., and Davis R.J. *Proc. Nat. Acad. Sci. USA* 15 94:7337-7342, 1997). JNKK2 specifically phosphorylates JNK, whereas JNKK1 can also phosphorylate and activate p38. Both JNKK1 and JNKK2 are widely expressed in mammalian tissues. JNKK1 and JNKK2 are activated by the MAPKKK enzymes, MEKK1 and 2 (Lange-Carter C.A., Pleiman C.M., Gardner A.M., Blumer K.J., and Johnson G.L. *Science* 260:315-319, 1993; Yan M., Dai J.C., Deak J.C., Kyriakis J.M., Zon L.I., Woodgett 20 J.R., and Templeton D.J. *Nature* 372:798-781, 1994). Both MEKK1 and MEKK2 are widely expressed in mammalian tissues.

Activation of the JNK pathway has been documented in a number of disease settings, providing the rationale for targeting this pathway for drug discovery. In addition, molecular genetic approaches have validated the pathogenic role of this pathway in several 25 diseases. For example, autoimmune and inflammatory diseases arise from the over-activation of the immune system. Activated immune cells express many genes encoding inflammatory molecules, including cytokines, growth factors, cell surface receptors, cell adhesion molecules and degradative enzymes. Many of these genes are regulated by the JNK pathway, through activation of the transcription factors AP-1 and ATF-2, including 30 TNF $\alpha$ , IL-2, E-selectin and matrix metalloproteinases such as collagenase-1 (Manning A.M. and Mercurio F. *Exp. Opin Invest. Drugs* 6: 555-567, 1997). Monocytes, tissue macrophages and tissue mast cells are key sources of TNF $\alpha$  production. The JNK pathway regulates TNF $\alpha$  production in bacterial lipopolysaccharide-stimulated macrophages, and in mast cells stimulated through the Fc $\epsilon$ R2 receptor (Swantek J.L., Cobb M.H., Geppert T.D. 35 *Mol. Cell. Biol.* 17:6274-6282, 1997; Ishizuka T., Tereda N., Gerwins P., Hamelmann E., Oshiba A., Fanger G.R., Johnson G.L., and Gelfand E.W. *Proc. Nat. Acad. Sci. USA* 94:6358-6363, 1997). Inhibition of JNK activation effectively modulates TNF $\alpha$  secretion from these cells. The JNK pathway therefore regulates production of this key pro-inflammatory cytokine. Matrix metalloproteinases (MMPs) promote cartilage and bone

erosion in rheumatoid arthritis, and generalized tissue destruction in other autoimmune diseases. Inducible expression of MMPs, including MMP-3 and MMP-9, type II and IV collagenases, are regulated via activation of the JNK pathway and AP-1 (Gum R., Wang H., Lengyel E., Juarez J., and Boyd D). *Oncogene* 14:1481-1493, 1997). In human rheumatoid synoviocytes activated with TNF $\alpha$ , IL-1, or Fas ligand the JNK pathway is activated (Han Z., Boyle D.L., Aupperle K.R., Bennett B., Manning A.M., Firestein G.S. *J. Pharm. Exp. Therap.* 291:1-7, 1999; Okamoto K., Fujisawa K., Hasunuma T., Kobata T., Sumida T., and Nishioka K. *Arth & Rheum* 40: 919-26, 1997). Inhibition of JNK activation results in decreased AP-1 activation and collagenase-1 expression (Han et al., *supra*). The JNK pathway therefore regulates MMP expression in cells involved in rheumatoid arthritis.

Inappropriate activation of T lymphocytes initiates and perpetuates many autoimmune diseases, including asthma, inflammatory bowel disease and multiple sclerosis. The JNK pathway is activated in T cells by antigen stimulation and CD28 receptor co-stimulation and regulates production of the growth factor IL-2 and cellular proliferation (Su B., Jacinto E., Hibi M., Kallunki T., Karin M., Ben-Neriah Y. *Cell* 77:727-736, 1994; Faris M., Kokot N., Lee L., and Nel A.E. *J. Biol. Chem.* 271:27366-27373, 1996). Peripheral T cells from mice genetically deficient in JNKK1 show decreased proliferation and IL-2 production after CD28 co-stimulation and PMA / Ca<sup>2+</sup> ionophore activation, providing important validation for the role of the JNK pathway in these cells (Nishina H., Bachmann M., Oliveria-dos-Santos A.J., et al. *J. Exp. Med.* 186: 941-953, 1997). It is known that T cells activated by antigen receptor stimulation in the absence of accessory cell-derived co-stimulatory signals lose the capacity to synthesize IL-2, a state called clonal anergy. This is an important process by which auto-reactive T cell populations are eliminated from the peripheral circulation. Of note, anergic T cells fail to activate the JNK pathway in response to CD3- and CD28-receptor co-stimulation, even though expression of the JNK enzymes is unchanged (Li W., Whaley C.D., Mondino A., and Mueller D.L. *Science* 271: 1272-1276, 1996). Recently, the examination of JNK-deficient mice revealed that the JNK pathway plays a key role in T cell activation and differentiation to T helper 1 and 2 cell types. JNK1 or JNK2 knockout mice develop normally and are phenotypically unremarkable. Activated naive CD4<sup>+</sup> T cells from these mice fail to produce IL-2 and do not proliferate well (Sabapathy, K., Hu, Y., Kallunki, T., Schreiber, M., David, J-P, Jochum, W., Wagner, E., Karin, M. *Curr Biol* 9:116-125, 1999). It is possible to induce T cell differentiation in T cells from these mice, generating Th1 cells (producers of IFN- $\gamma$  and TNF $\beta$ ) and Th2 effector cells (producers of IL-4, IL-5, IL-6, IL-10 and IL-13). Deletion of either JNK1 or JNK2 in mice resulted in a selective defect in the ability of Th1 effector cells to express

5 IFN $\gamma$ . This suggests that JNK1 and JNK2 do not have redundant functions in T cells and that they play different roles in the control of cell growth, differentiation and death. The JNK pathway therefore, is an important point for regulation of T cell responses to antigen.

Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) have a prominent role in the pathogenesis of anorexia and cachexia of chronic diseases.

10 Pentoxifylline is an inhibitor of TNF-alpha which has been tested as a therapeutic in the treatment of cachexia. Studies with pentoxifylline have not shown efficacy in reversing weight-loss despite evidence of TNF-alpha inhibition (Haslett, P.A., 1998, Semin. Oncol. 25:53-7).

## 2.2 DISEASE-RELATED WASTING

15 A side-effect of some acute or chronic diseases is wasting, a loss of physical bulk through the breakdown of bodily tissue. Examples of some clinically important types of wasting follow.

### 2.2.1 End-Stage Renal Disease-Related Wasting

Protein and calorie (energy) malnutrition, which occurs commonly inpatients  
20 with end-stage renal disease and is associated with an increase in morbidity and mortality (Hakim, R.M. et al., 1993 Am. J. Kidney Dis. 21:125-37; Chen, Y. et al., 2001, J. Ren. Nutr. 11:62-6), can result in end-stage renal disease-related wasting. The prevalence of malnutrition in the chronic dialysis population ranges from 10-54% depending on the parameter measured, and clinicians have long recognized that malnourished dialysis patients  
25 had a poorer prognosis than non-malnourished patients (Don, B.R., 2000, J. of Nephrology 13:249-59).

### 2.2.2 Cancer-Related Wasting

Fatigue is the most frequently reported symptom by cancer patients. Skeletal muscle wasting, which occurs as part of cancer cachexia, is one of the mechanisms that  
30 contribute to fatigue. Cancer-induced skeletal muscle wasting can occur despite normal food intake and is not prevented by nutritional supplementation (al-Majid, S. and McCarthy, D.O., 2001, Biol. Res. Nurs. 2:186-97).

The cancer anorexia-cachexia syndrome is one of the most common causes of death among cancer patients and is present in 80% at death. Tumors produce both direct  
35 and indirect abnormalities which result in anorexia and weight loss. There is no current treatment to control or reverse the process (Horvitz, H.R., 2000, Semin. Oncol. 27:64-8).

### 2.2.3 HIV- and/or AIDS-Related wasting

Progressive, unintentional weight loss is a common complication of HIV which often produces malnutrition leading to wasting and cachexia. Although it can occur at any point during the course of HIV, severe weight loss more frequently occurs late in the disease process (Cianfrocca, M. and Von Roenn, J.H., 1997, AIDS Patient Care and STDs 11:259-267). The severe weight loss can be defined as "profound involuntary weight loss greater than 10% of baseline body weight plus either chronic diarrhea, chronic weakness or documented fever in the absence of a concurrent illness or condition that could explain these findings (Centers for Disease Control, MMWR, 1987, 36: 3S-15S). AIDS patients who experience weight loss beyond a certain percentage of ideal body weight are at greater risk of death, thereby establishing a link between survival and the extent of body cell mass depletion (Chlebowski, R.T., 1989, Am. J. Gastroenterol. 84:1288). Consequently, treating or preventing HIV- and/or AIDS-related wasting should improve the life-expectancy and quality of life. However, traditional approaches have proved to be difficult and the outcome of nutritional supplementation is poor, with the tendency for weight gain to be fat and water and not lean tissue (Chang, H.R., 1999, Nutrition 14:853-863).

Body-composition associated with weight loss and HIV differs from that seen as a result of starvation in that starvation-associated weight loss is characterized by increased fat catabolism with relative sparing of lean body tissue as opposed to HIV-related wasting which is characterized by significant depletion of lean body mass (Cahill G.S., N. Eng. J. of Med. 282: 668-691). Loss of lean body mass is particularly prominent in association with secondary infections (Kotler, D.P. et al. Am. J. Clin. Nutr. 42:1255-1265). Additionally, malnutrition has deleterious effects on immune function, including changes in cell-mediated immunity and in neutrophil and complement function (Chandra R.K., 1983, Lancet 1:688-691).

The abnormal cytokine environment associated with HIV and its related complications has been implicated in the pathogenesis of AIDS-related wasting (Cianfrocca, M. and Von Roenn, J.H., 1997, AIDS Patient Care and STDs 11:259-267). Cytokine-mediated alterations in host-metabolism likely play an important therapeutic role in HIV-associated anorexia and cachexia. Experimental treatment with inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-1 (IL-1), or interferon (IFN) *in vivo* or *in vitro* can produce striking anorexia (Tracey, K.J. and Cerami, A., 1994, Ann. Rev. Med. 45:491:503; Hellerstein, M.K. et al., 1989, J. Clin. Invest. 84:228-235; Spiegel, R.J., 1987, Sem. Oncol. 14:1-12). Moreover, administration of TNF and IL-1 to experimental animals have been found to produce skeletal muscle catabolism, the effects of which were found to

5 be independent from and additive to those resulting from semi-starvation (Ling, P.R. et al., 1996, Am. J. Physiol. 270:E305; Ling P.R., et al., 1997, Am. J. Physiol. 272:E333). Additionally, interference with TNF production by anti-TNF antibodies blocks muscle proteolysis *in vivo* (Costelli, P., 1993, J. Clin. Invest. 92:2783).

10 Currently available preventative and therapeutic approaches for treating HIV- and/or AIDS-related wasting include baseline nutritional assessment, early diagnosis of malnutrition and maintenance of adequate nutritional intake, early diagnosis and prevention of opportunistic infections, appetite stimulants and anabolic hormonal therapy. However, none of these approaches has been shown to treat or prevent HIV- and/or AIDS-related wasting.

#### 15 2.2.4 Chronic Disease-Related Wasting

Body wasting is a common feature of several chronic diseases (Pichard C, Kyle U.G., 1998, Curr. Opin. Clin. Nutr. Metab. Care. 1:357-61). Chronic diseases, other than those discussed above, which wasting is associated with are tuberculosis (Schwenk, A., 2000, Curr. Opin. Clin. Nutr. Metab. Care 3:285-91), chronic obstructive pulmonary disease (Farber, M.O., 2000, Neurol. Clin. 18:245-62), chronic heart failure (Franssen F.M., 2002, Clin. Nutr. 21:1-14), rheumatoid arthritis, chronic inflammatory diseases (*e.g.*, scleroderma or mixed connective tissue disease) and chronic infectious diseases (*e.g.*, osteoarthritis and bacterial endocarditis).

25 Accordingly, there is a need in the art for compounds useful in the treatment or prevention of disease-related wasting. In addition, there is a need for pharmaceutical compositions and methods useful in the treatment or prevention of disease-related wasting. The present invention fulfills these needs, and provides further related advantages.

Citation of any reference in Section 2 of this application is not an admission that the reference is prior art to the application.

### 30 3. SUMMARY OF THE INVENTION

The present invention provides methods useful for treating or preventing disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor. In one embodiment, the disease is HIV. In another embodiment, the disease is AIDS. In another embodiment, the disease is cancer. In another embodiment, the disease is end-stage renal disease. In another embodiment, the disease is kidney failure. In another embodiment, the disease is chronic heart disease. In another embodiment, the disease is obstructive pulmonary disease. In another embodiment, the disease is tuberculosis. In another embodiment, the disease is rheumatoid arthritis. In

5 another embodiment, the disease is a chronic inflammatory disease including, but not limited to, scleroderma and mixed connective tissue disease. In another embodiment, the disease is a chronic infectious disease including, but not limited to, osteoarthritis and bacterial endocarditis.

The present invention also provides methods useful for treating or preventing  
10 disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor and an effective amount of a therapeutic or prophylactic agent. The therapeutic or prophylactic agents include, but are not limited to, those useful in the treatment or prevention of HIV, AIDS, cancer, rheumatoid arthritis, chronic infections (*e.g.*, tuberculosis, osteoarthritis and bacterial endocarditis), chronic  
15 inflammatory diseases (*e.g.*, scleroderma and mixed connective tissue disease), end-stage renal disease, kidney failure, chronic heart disease or obstructive pulmonary disease. Such methods and regimens can encompass concurrent, sequential, synchronized or alternating/cyclic administration of a JNK Inhibitor with the therapeutic or prophylactic agent.

### 20 3.1 DEFINITIONS

As used herein, the term "patient" means an animal (*e.g.*, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig), preferably a mammal such as a non-primate and a primate (*e.g.*, monkey and human), most preferably a human.

"Alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon  
25 having from 1 to 10 carbon atoms. "Lower alkyl" means alkyl, as defined above, having from 1 to 4 carbon atoms. Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl,  
30 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimethylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like.

An "alkenyl group" or "alkylidene" mean a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-

5 carbon double bond. Representative straight chain and branched (C<sub>2</sub>-C<sub>10</sub>)alkenyls include - vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like. An alkenyl group can  
10 be unsubstituted or substituted. A "cyclic alkylidene" is a ring having from 3 to 8 carbon atoms and including at least one carbon-carbon double bond, wherein the ring can have from 1 to 3 heteroatoms.

An "alkynyl group" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon  
15 triple bond. Representative straight chain and branched -(C<sub>2</sub>-C<sub>10</sub>)alkynyls include - acetylenyl, -propynyl, -1-butylnyl, -2-butylnyl, -1-pentylnyl, -2-pentylnyl, -3-methyl-1-butylnyl, -4-pentylnyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonylnyl, -2-nonylnyl, -8-nonylnyl, -1-decynyl, -2-decynyl, -9-decynyl, and the like. An alkynyl group can be unsubstituted or  
20 substituted.

The terms "Halogen" and "Halo" mean fluorine, chlorine, bromine or iodine.

"Haloalkyl" means an alkyl group, wherein alkyl is defined above, substituted with one or more halogen atoms.

"Keto" means a carbonyl group (*i.e.*, C=O).

25 "Acyl" means an -C(O)alkyl group, wherein alkyl is defined above, including -C(O)CH<sub>3</sub>, -C(O)CH<sub>2</sub>CH<sub>3</sub>, -C(O)(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -C(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -C(O)(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -C(O)(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

"Acyloxy" means an -OC(O)alkyl group, wherein alkyl is defined above, including -OC(O)CH<sub>3</sub>, -OC(O)CH<sub>2</sub>CH<sub>3</sub>, -OC(O)(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -OC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -  
30 OC(O)(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -OC(O)(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

"Ester" means an -C(O)Oalkyl group, wherein alkyl is defined above, including -C(O)OCH<sub>3</sub>, -C(O)OCH<sub>2</sub>CH<sub>3</sub>, -C(O)O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -C(O)O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -C(O)O(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -C(O)O(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

"Alkoxy" means -O-(alkyl), wherein alkyl is defined above, including -  
35 OCH<sub>3</sub>, -OCH<sub>2</sub>CH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like. "Lower alkoxy" means -O-(lower alkyl), wherein lower alkyl is as described above.

"Alkoxyalkoxy" means -O-(alkyl)-O-(alkyl), wherein each alkyl is independently an alkyl group defined above, including -OCH<sub>2</sub>OCH<sub>3</sub>, -OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, and the like.

5 “Alkoxycarbonyl” means  $-C(=O)O-(\text{alkyl})$ , wherein alkyl is defined above, including  $-C(=O)O-CH_3$ ,  $-C(=O)O-CH_2CH_3$ ,  $-C(=O)O-(CH_2)_2CH_3$ ,  $-C(=O)O-(CH_2)_3CH_3$ ,  $-C(=O)O-(CH_2)_4CH_3$ ,  $-C(=O)O-(CH_2)_5CH_3$ , and the like.

“Alkoxycarbonylalkyl” means  $-(\text{alkyl})-C(=O)O-(\text{alkyl})$ , wherein each alkyl is independently defined above, including  $-CH_2-C(=O)O-CH_3$ ,  $-CH_2-C(=O)O-CH_2CH_3$ ,  $-CH_2-C(=O)O-(CH_2)_2CH_3$ ,  $-CH_2-C(=O)O-(CH_2)_3CH_3$ ,  $-CH_2-C(=O)O-(CH_2)_4CH_3$ ,  $-CH_2-C(=O)O-(CH_2)_5CH_3$ , and the like.

“Alkoxyalkyl” means  $-(\text{alkyl})-O-(\text{alkyl})$ , wherein each alkyl is independently an alkyl group defined above, including  $-CH_2OCH_3$ ,  $-CH_2OCH_2CH_3$ ,  $-(CH_2)_2OCH_2CH_3$ ,  $-(CH_2)_2O(CH_2)_2CH_3$ , and the like.

15 “Aryl” means a carbocyclic aromatic group containing from 5 to 10 ring atoms. Representative examples include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, pyridinyl and naphthyl, as well as benzo-fused carbocyclic moieties including 5,6,7,8-tetrahydronaphthyl. A carbocyclic aromatic group can be unsubstituted or substituted. In one embodiment, the carbocyclic aromatic group is a phenyl group.

“Aryloxy” means  $-O-\text{aryl}$  group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted. In one embodiment, the aryl ring of an aryloxy group is a phenyl group

25 “Arylalkyl” means  $-(\text{alkyl})-(\text{aryl})$ , wherein alkyl and aryl are as defined above, including  $-(CH_2)\text{phenyl}$ ,  $-(CH_2)_2\text{phenyl}$ ,  $-(CH_2)_3\text{phenyl}$ ,  $-CH(\text{phenyl})_2$ ,  $-CH(\text{phenyl})_3$ ,  $-(CH_2)\text{tolyl}$ ,  $-(CH_2)\text{anthracenyl}$ ,  $-(CH_2)\text{fluorenyl}$ ,  $-(CH_2)\text{indenyl}$ ,  $-(CH_2)\text{azulenyl}$ ,  $-(CH_2)\text{pyridinyl}$ ,  $-(CH_2)\text{naphthyl}$ , and the like.

“Arylalkyloxy” means  $-O-(\text{alkyl})-(\text{aryl})$ , wherein alkyl and aryl are defined above, including  $-O-(CH_2)_2\text{phenyl}$ ,  $-O-(CH_2)_3\text{phenyl}$ ,  $-O-CH(\text{phenyl})_2$ ,  $-O-CH(\text{phenyl})_3$ ,  $-O-(CH_2)\text{tolyl}$ ,  $-O-(CH_2)\text{anthracenyl}$ ,  $-O-(CH_2)\text{fluorenyl}$ ,  $-O-(CH_2)\text{indenyl}$ ,  $-O-(CH_2)\text{azulenyl}$ ,  $-O-(CH_2)\text{pyridinyl}$ ,  $-O-(CH_2)\text{naphthyl}$ , and the like.

35 “Aryloxyalkyl” means  $-(\text{alkyl})-O-(\text{aryl})$ , wherein alkyl and aryl are defined above, including  $-CH_2-O-(\text{phenyl})$ ,  $-(CH_2)_2-O-\text{phenyl}$ ,  $-(CH_2)_3-O-\text{phenyl}$ ,  $-(CH_2)-O-\text{tolyl}$ ,  $-(CH_2)-O-\text{anthracenyl}$ ,  $-(CH_2)-O-\text{fluorenyl}$ ,  $-(CH_2)-O-\text{indenyl}$ ,  $-(CH_2)-O-\text{azulenyl}$ ,  $-(CH_2)-O-\text{pyridinyl}$ ,  $-(CH_2)-O-\text{naphthyl}$ , and the like.

“Cycloalkyl” means a monocyclic or polycyclic saturated ring having carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to,  $(C_3-C_7)$ cycloalkyl groups, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic

5 terpenes. A cycloalkyl group can be unsubstituted or substituted. In one embodiment, the cycloalkyl group is a monocyclic ring or bicyclic ring.

"Cycloalkyloxy" means -O-(cycloalkyl), wherein cycloalkyl is defined above, including -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl, -O-cyclohexyl, -O-cycloheptyl and the like.

10 "Cycloalkylalkyloxy" means -O-(alkyl)-(cycloalkyl), wherein cycloalkyl and alkyl are defined above, including -O-CH<sub>2</sub>-cyclopropyl, -O-(CH<sub>2</sub>)<sub>2</sub>-cyclopropyl, -O-(CH<sub>2</sub>)<sub>3</sub>-cyclopropyl, -O-(CH<sub>2</sub>)<sub>4</sub>-cyclopropyl, -O-CH<sub>2</sub>-cyclobutyl, -O-CH<sub>2</sub>-cyclopentyl, -O-CH<sub>2</sub>-cyclohexyl, -O-CH<sub>2</sub>-cycloheptyl, and the like.

15 "Aminoalkoxy" means -O-(alkyl)-NH<sub>2</sub>, wherein alkyl is defined above, such as -O-CH<sub>2</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>2</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>3</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>4</sub>-NH<sub>2</sub>, -O-(CH<sub>2</sub>)<sub>5</sub>-NH<sub>2</sub>, and the like.

"Mono-alkylamino" means -NH(alkyl), wherein alkyl is defined above, such as -NHCH<sub>3</sub>, -NHCH<sub>2</sub>CH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -NH(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

20 "Di-alkylamino" means -N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N((CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), and the like.

25 "Mono-alkylaminoalkoxy" means -O-(alkyl)-NH(alkyl), wherein each alkyl is independently an alkyl group defined above, including -O-(CH<sub>2</sub>)-NHCH<sub>3</sub>, -O-(CH<sub>2</sub>)-NHCH<sub>2</sub>CH<sub>3</sub>, -O-(CH<sub>2</sub>)-NH(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -O-(CH<sub>2</sub>)-NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -O-(CH<sub>2</sub>)-NH(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -O-(CH<sub>2</sub>)-NH(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, -O-(CH<sub>2</sub>)<sub>2</sub>-NHCH<sub>3</sub>, and the like.

"Di-alkylaminoalkoxy" means -O-(alkyl)-N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including -O-(CH<sub>2</sub>)-N(CH<sub>3</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)-N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)-N((CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -O-(CH<sub>2</sub>)-N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), and the like.

30 "Arylamino" means -NH(aryl), wherein aryl is defined above, including -NH(phenyl), -NH(tolyl), -NH(anthracenyl), -NH(flourenyl), -NH(indenyl), -NH(azulenyl), -NH(pyridinyl), -NH(naphthyl), and the like.

35 "Arylalkylamino" means -NH-(alkyl)-(aryl), wherein alkyl and aryl are defined above, including -NH-CH<sub>2</sub>-(phenyl), -NH-CH<sub>2</sub>-(tolyl), -NH-CH<sub>2</sub>-(anthracenyl), -NH-CH<sub>2</sub>-(flourenyl), -NH-CH<sub>2</sub>-(indenyl), -NH-CH<sub>2</sub>-(azulenyl), -NH-CH<sub>2</sub>-(pyridinyl), -NH-CH<sub>2</sub>-(naphthyl), -NH-(CH<sub>2</sub>)<sub>2</sub>-(phenyl) and the like.

"Alkylamino" means mono-alkylamino or di-alkylamino as defined above, such as -N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N((CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>) and -

5 N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N((CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>) and the like.

"Cycloalkylamino" means -NH-(cycloalkyl), wherein cycloalkyl is as defined above, including -NH-cyclopropyl, -NH-cyclobutyl, -NH-cyclopentyl, -NH-cyclohexyl, -NH-cycloheptyl, and the like.

10 "Carboxyl" and "carboxy" mean -COOH.

"Cycloalkylalkylamino" means -NH-(alkyl)-(cycloalkyl), wherein alkyl and cycloalkyl are defined above, including -NH-CH<sub>2</sub>-cyclopropyl, -NH-CH<sub>2</sub>-cyclobutyl, -NH-CH<sub>2</sub>-cyclopentyl, -NH-CH<sub>2</sub>-cyclohexyl, -NH-CH<sub>2</sub>-cycloheptyl, -NH-(CH<sub>2</sub>)<sub>2</sub>-cyclopropyl and the like.

15 "Aminoalkyl" means -(alkyl)-NH<sub>2</sub>, wherein alkyl is defined above, including CH<sub>2</sub>-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>2</sub>-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>3</sub>-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>4</sub>-NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>5</sub>-NH<sub>2</sub> and the like.

"Mono-alkylaminoalkyl" means -(alkyl)-NH(alkyl), wherein each alkyl is independently an alkyl group defined above, including -CH<sub>2</sub>-NH-CH<sub>3</sub>, -CH<sub>2</sub>-NHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>-NH(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>-NH(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -CH<sub>2</sub>-NH(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -CH<sub>2</sub>-NH(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, -  
20 (CH<sub>2</sub>)<sub>2</sub>-NH-CH<sub>3</sub>, and the like.

"Di-alkylaminoalkyl" means -(alkyl)-N(alkyl)(alkyl), wherein each alkyl is independently an alkyl group defined above, including -CH<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>-N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>-N((CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>-N(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>), -(CH<sub>2</sub>)<sub>2</sub>-N(CH<sub>3</sub>)<sub>2</sub>, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10 members and  
25 having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinoliny, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl,  
30 pyrimidinyl, pyrazinyl, triazinyl, cinnoliny, phthalazinyl, quinazolinyl, pyrimidyl, oxetanyl, azepinyl, piperazinyl, morpholinyl, dioxanyl, thietanyl and oxazolyl.

"Heteroarylalkyl" means -(alkyl)-(heteroaryl), wherein alkyl and heteroaryl are defined above, including -CH<sub>2</sub>-triazolyl, -CH<sub>2</sub>-tetrazolyl, -CH<sub>2</sub>-oxadiazolyl, -CH<sub>2</sub>-pyridyl, -CH<sub>2</sub>-furyl, -CH<sub>2</sub>-benzofuranyl, -CH<sub>2</sub>-thiophenyl, -CH<sub>2</sub>-benzothiophenyl, -CH<sub>2</sub>-quinoliny, -CH<sub>2</sub>-pyrrolyl, -CH<sub>2</sub>-indolyl, -CH<sub>2</sub>-oxazolyl, -CH<sub>2</sub>-benzoxazolyl, -CH<sub>2</sub>-imidazolyl, -CH<sub>2</sub>-benzimidazolyl, -CH<sub>2</sub>-thiazolyl, -CH<sub>2</sub>-benzothiazolyl, -CH<sub>2</sub>-isoxazolyl, -CH<sub>2</sub>-pyrazolyl, -CH<sub>2</sub>-isothiazolyl, -CH<sub>2</sub>-pyridazinyl, -CH<sub>2</sub>-pyrimidinyl, -CH<sub>2</sub>-pyrazinyl, -CH<sub>2</sub>-triazinyl, -CH<sub>2</sub>-cinnoliny, -CH<sub>2</sub>-phthalazinyl, -CH<sub>2</sub>-quinazolinyl, -CH<sub>2</sub>-pyrimidyl, -

5 CH<sub>2</sub>-oxetanyl, -CH<sub>2</sub>-azepinyl, -CH<sub>2</sub>-piperazinyl, -CH<sub>2</sub>-morpholinyl, -CH<sub>2</sub>-dioxanyl, -CH<sub>2</sub>-thietanyl, -CH<sub>2</sub>-oxazolyl, -(CH<sub>2</sub>)<sub>2</sub>-triazolyl, and the like.

“Heterocycle” means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the  
 10 nitrogen and sulfur heteroatoms can be optionally oxidized, and the nitrogen heteroatom can be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle can be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Representative heterocycles include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl,  
 15 oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

“Heterocycle fused to phenyl” means a heterocycle, wherein heterocycle is defined as above, that is attached to a phenyl ring at two adjacent carbon atoms of the  
 20 phenyl ring.

“Heterocycloalkyl” means -(alkyl)-(heterocycle), wherein alkyl and heterocycle are defined above, including -CH<sub>2</sub>-morpholinyl, -CH<sub>2</sub>-pyrrolidinonyl, -CH<sub>2</sub>-pyrrolidinyl, -CH<sub>2</sub>-piperidinyl, -CH<sub>2</sub>-hydantoinyl, -CH<sub>2</sub>-valerolactamyl, -CH<sub>2</sub>-oxiranyl, -CH<sub>2</sub>-oxetanyl, -CH<sub>2</sub>-tetrahydrofuranyl, -CH<sub>2</sub>-tetrahydropyranyl, -CH<sub>2</sub>-tetrahydropyridinyl, -  
 25 CH<sub>2</sub>-tetrahydropyrimidinyl, -CH<sub>2</sub>-tetrahydrothiophenyl, -CH<sub>2</sub>-tetrahydrothiopyranyl, -CH<sub>2</sub>-tetrahydropyrimidinyl, -CH<sub>2</sub>-tetrahydrothiophenyl, -CH<sub>2</sub>-tetrahydrothiopyranyl, and the like.

The term “substituted” as used herein means any of the above groups (*i.e.*, aryl, arylalkyl, heterocycle and heterocycloalkyl) wherein at least one hydrogen atom of the  
 30 moiety being substituted is replaced with a substituent. In one embodiment, each carbon atom of the group being substituted is substituted with no more than two substituents. In another embodiment, each carbon atom of the group being substituted is substituted with no more than one substituent. In the case of a keto substituent, two hydrogen atoms are replaced with an oxygen which is attached to the carbon via a double bond. Substituents  
 35 include halogen, hydroxyl, alkyl, haloalkyl, mono- or di-substituted aminoalkyl, alkyloxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -NR<sub>a</sub>R<sub>b</sub>, -NR<sub>a</sub>C(=O)R<sub>b</sub>, -NR<sub>a</sub>C(=O)NR<sub>a</sub>R<sub>b</sub>, -NR<sub>a</sub>C(=O)OR<sub>b</sub>, -NR<sub>a</sub>SO<sub>2</sub>R<sub>b</sub>, -OR<sub>a</sub>, -C(=O)R<sub>a</sub>, -C(=O)OR<sub>a</sub>, -C(=O)NR<sub>a</sub>R<sub>b</sub>, -OC(=O)R<sub>a</sub>, -OC(=O)OR<sub>a</sub>, -OC(=O)NR<sub>a</sub>R<sub>b</sub>, -NR<sub>a</sub>SO<sub>2</sub>R<sub>b</sub>, or a radical of the formula -Y-Z-R<sub>a</sub> where Y is alkanediyl, or a direct bond, Z is -O-, -S-, -N(R<sub>b</sub>)-, -C(=O)-, -C(=O)O-, -

5 OC(=O)-, -N(R<sub>b</sub>)C(=O)-, -C(=O)N(R<sub>b</sub>)- or a direct bond, wherein R<sub>a</sub> and R<sub>b</sub> are the same or different and independently hydrogen, amino, alkyl, haloalkyl, aryl, arylalkyl, heterocycle, or heterocylealkyl, or wherein R<sub>a</sub> and R<sub>b</sub> taken together with the nitrogen atom to which they are attached form a heterocycle.

10 "Haloalkyl" means alkyl, wherein alkyl is defined as above, having one or more hydrogen atoms replaced with halogen, wherein halogen is as defined above, including -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>F, -CBr<sub>3</sub>, -CHBr<sub>2</sub>, -CH<sub>2</sub>Br, -CCl<sub>3</sub>, -CHCl<sub>2</sub>, -CH<sub>2</sub>Cl, -Cl<sub>3</sub>, -CHI<sub>2</sub>, -CH<sub>2</sub>I, -CH<sub>2</sub>-CF<sub>3</sub>, -CH<sub>2</sub>-CHF<sub>2</sub>, -CH<sub>2</sub>-CH<sub>2</sub>F, -CH<sub>2</sub>-CBr<sub>3</sub>, -CH<sub>2</sub>-CHBr<sub>2</sub>, -CH<sub>2</sub>-CH<sub>2</sub>Br, -CH<sub>2</sub>-CCl<sub>3</sub>, -CH<sub>2</sub>-CHCl<sub>2</sub>, -CH<sub>2</sub>-CH<sub>2</sub>Cl, -CH<sub>2</sub>-Cl<sub>3</sub>, -CH<sub>2</sub>-CHI<sub>2</sub>, -CH<sub>2</sub>-CH<sub>2</sub>I, and the like.

15 "Hydroxyalkyl" means alkyl, wherein alkyl is as defined above, having one or more hydrogen atoms replaced with hydroxy, including -CH<sub>2</sub>OH, -CH<sub>2</sub>CH<sub>2</sub>OH, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>OH, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>2</sub>OH, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>2</sub>OH, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>2</sub>OH, -CH(OH)-CH<sub>3</sub>, -CH<sub>2</sub>CH(OH)CH<sub>3</sub>, and the like.

"Hydroxy" means -OH.

"Sulfonyl" means -SO<sub>3</sub>H.

20 "Sulfonylalkyl" means -SO<sub>2</sub>-(alkyl), wherein alkyl is defined above, including -SO<sub>2</sub>-CH<sub>3</sub>, -SO<sub>2</sub>-CH<sub>2</sub>CH<sub>3</sub>, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -SO<sub>2</sub>-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

"Sulfinylalkyl" means -SO-(alkyl), wherein alkyl is defined above, including -SO-CH<sub>3</sub>, -SO-CH<sub>2</sub>CH<sub>3</sub>, -SO-(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -SO-(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -SO-(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -SO-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

"Sulfonamidoalkyl" means -NHSO<sub>2</sub>-(alkyl), wherein alkyl is defined above, including -NHSO<sub>2</sub>-CH<sub>3</sub>, -NHSO<sub>2</sub>-CH<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>-(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -NHSO<sub>2</sub>-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

30 "Thioalkyl" means -S-(alkyl), wherein alkyl is defined above, including -S-CH<sub>3</sub>, -S-CH<sub>2</sub>CH<sub>3</sub>, -S-(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -S-(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -S-(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -S-(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, and the like.

As used herein, the term "JNK Inhibitor" means a compound capable of inhibiting the activity of JNK *in vitro* or *in vivo*. The JNK Inhibitor can be in the form of a pharmaceutically acceptable salt, free base, solvate, hydrate, stereoisomer, clathrate or prodrug thereof. Such inhibitory activity can be determined by an assay or animal model well-known in the art including those set forth in Section 5. In one embodiment, the JNK Inhibitor is a compound of structure (I)-(III).

"JNK" means a protein or an isoform thereof expressed by a JNK 1, JNK 2, or JNK 3 gene (Gupta, S., Barrett, T., Whitmarsh, A.J., Cavanagh, J., Sluss, H.K., Derijard, B. and Davis, R.J. *The EMBO J.* 15:2760-2770, 1996).

5 As used herein, the phrase "an effective amount" when used in connection with a JNK Inhibitor means an amount of the JNK Inhibitor that is useful for for treating or preventing disease-related wasting.

As used herein, the phrase "an effective amount" when used in connection with a therapeutic or prophylactic agent means an amount of the therapeutic or prophylactic agent that is useful for for treating or preventing disease-related wasting when administered while the JNK Inhibitor exerts its activity.

As used herein, the term "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the JNK Inhibitor include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of specific salts thus include hydrochloride and mesylate salts. Others are well-known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18<sup>th</sup> eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19<sup>th</sup> eds., Mack Publishing, Easton PA (1995).

As used herein and unless otherwise indicated, the term "polymorph" means a particular crystalline arrangement of the JNK Inhibitor. Polymorphs can be obtained through the use of different work-up conditions and/or solvents. In particular, polymorphs can be prepared by recrystallization of a JNK Inhibitor in a particular solvent.

As used herein and unless otherwise indicated, the term "prodrug" means a JNK Inhibitor derivative that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound, particularly a JNK Inhibitor. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a JNK Inhibitor that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates,

5 biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by *Burger's Medicinal Chemistry and Drug*  
10 *Discovery* 6<sup>th</sup> ed. (Donald J. Abraham *ed.*, 2001, Wiley) and *Design and Application of Prodrugs* (H. Bundgaard *ed.*, 1985, Harwood Academic Publishers Gmfb).

As used herein and unless otherwise indicated, the term "optically pure" or "stereomerically pure" means one stereoisomer of a compound is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having  
15 one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about  
20 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other  
25 stereoisomers of the compound.

"Component of the JNK pathway" means any biological molecule that has a direct or indirect effect on the activity of JNK.

As used herein, "HIV therapy" or "AIDS therapy" refers to a therapeutic protocol used to treat HIV or AIDS or HIV/AIDS related symptoms comprising  
30 administering an agent useful in treating HIV or AIDS including, but not limited to, a reverse transcriptase inhibitor and/or a protease inhibitor. In certain embodiments, the AIDS therapeutic agent is a protease inhibitor including, but not limited to: amprenavir (sold as a formulation under the trade name AGNERASE); nelfinavir (sold as a formulation under the trade name VIRACEPT); saquinavir (sold as a formulation under the trade name  
35 FORTOVASE); indinavir (sold as a formulation under the trade name CRIXIVAN); saquinavir (sold as a formulation under the trade name INVIRASE); lopinavir (sold as a formulation under the trade name KALETRA); ritonavir (sold as a formulation under the trade name NORVIR); or GW433908. In other certain embodiments, the AIDS therapeutic agent is a reverse transcriptase inhibitor including, but not limited to: a composition

5 comprising 3TC and lamivudine (sold as a formulation under the trade name EPIVIR); a composition comprising ddC and zalcitabine (sold as a formulation under the trade name HIVID); delavirdine (sold as a formulation under the trade name RESCRIPTOR); zidovudine (sold as a formulation under the trade name RETROVIR); efavirenz (sold as a formulation under the trade name SUSTIVA); a composition comprising abacavir,  
10 zidovudine and lamivudine (sold as a formulation under the trade name TRIZIVIR); a composition comprising ddI and didanosine (sold as a formulation under the trade name VIDEX); nevirapine (sold as a formulation under the trade name VIRAMUNE); tenofovir disoproxil fumarate (sold as a formulation under the trade name VIREAD); a composition comprising d4t and stavudine (sold as a formulation under the trade name ZERIT); or  
15 abacavir (sold as a formulation under the trade name ZIAGEN).

As used herein in connection with the term "therapeutic agent", "therapeutically effective amount" includes the amount of the therapeutic agent sufficient to delay or minimize symptoms associated with disease-related wasting. A therapeutically effective amount also includes the amount of the therapeutic agent that provides a  
20 therapeutic benefit in the treatment or management of disease-related wasting.

As used herein, the term "prophylactic agent" includes any agent that can be used in the prevention of a disease (*e.g.*, HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease, tuberculosis, rheumatoid arthritis, a chronic inflammatory disease, scleroderma, a mixed connective tissue disease, a  
25 chronic infectious disease, osteoarthritis or bacterial endocarditis).

As used herein, the term "therapeutic agent" includes any agent(s) that can be used in the treatment of a disease (*e.g.*, HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease, tuberculosis, rheumatoid arthritis, a chronic inflammatory disease, scleroderma, a mixed connective  
30 tissue disease, a chronic infectious disease, osteoarthritis or bacterial endocarditis).

In one embodiment, the disease is HIV or AIDS and the prophylactic or therapeutic agents include amprenavir (sold as a formulation under the trade name AGNERASE); nelfinavir (sold as a formulation under the trade name VIRACEPT); saquinavir (sold as a formulation under the trade name FORTOVASE); indinavir (sold as a  
35 formulation under the trade name CRIXIVAN); saquinavir (sold as a formulation under the trade name INVIRASE); lopinavir (sold as a formulation under the trade name KALETRA); ritonavir (sold as a formulation under the trade name NORVIR); or GW433908. In other certain embodiments, the AIDS therapeutic agent is a reverse transcriptase inhibitor including, but not limited to: a composition comprising 3TC and lamivudine (sold as a

5 formulation under the trade name EPIVIR); a composition comprising ddC and zalcitabine (sold as a formulation under the trade name HIVID); delavirdine (sold as a formulation under the trade name RESCRIPTOR); zidovudine (sold as a formulation under the trade name RETROVIR); efavirenz (sold as a formulation under the trade name SUSTIVA); a composition comprising abacavir, zidovudine and lamivudine (sold as a formulation under the trade name TRIZIVIR); a composition comprising ddI and didanosine (sold as a formulation under the trade name VIDEX); nevirapine (sold as a formulation under the trade name VIRAMUNE); tenofovir disoproxil fumarate (sold as a formulation under the trade name VIREAD); a composition comprising d4t and stavudine (sold as a formulation under the trade name ZERIT); or abacavir (sold as a formulation under the trade name ZIAGEN).

In one embodiment, the disease is end-stage renal disease and the prophylactic or therapeutic agents include angiotensin II, cisplatin, dialysis and lisinopril.

In one embodiment, the disease is kidney failure and the prophylactic or therapeutic agents include angiotensin II, cisplatin, dialysis and lisinopril.

20 In one embodiment, the disease is cancer and the prophylactic or therapeutic agents include paclitaxel, irinotecan, camptothecin, cyclophosphamide, 5-fluorouracil, cisplatin, carboplatin, methotrexate, trimetrexate, erbitux, thalidomide, actimid and revimid.

In one embodiment, the disease is chronic heart disease and the prophylactic or therapeutic agents include perindopril.

In one embodiment, the disease is obstructive pulmonary disease and the prophylactic or therapeutic agents include budesonide, prednisolone, beta(2)-agonists, ipratropium bromide and oral antibiotics.

In one embodiment, the disease is a chronic infectious disease.

30 In one embodiment, the disease is a chronic inflammatory disease.

In one embodiment, the disease is tuberculosis and the prophylactic or therapeutic agents include infliximab, rifampicin and streptomycin.

As used herein, the phrase "non-responsive/refractory" is used to describe a condition of patients treated with currently available HIV, AIDS, end-stage renal disease, kidney failure, cancer, chronic heart disease, obstructive pulmonary disease, chronic infectious diseases (*e.g.*, osteoarthritis and bacterial endocarditis), chronic inflammatory diseases (*e.g.*, scleroderma and mixed connective tissue disease) or tuberculosis therapies wherein the therapy is not clinically adequate to treat the patients such that these patients

5 need additional effective therapy, e.g., remain unsusceptible to therapy. The phrase includes a condition of patients who respond to therapy yet suffer from side effects.

As used herein, the phrase "low tolerance" refers to a state in which the patient suffers from side effects from treatment so that the patient does not benefit from and/or will not continue therapy because of its adverse effects.

10 As used herein, the term "potentiate" refers to an improvement in the efficacy of a therapeutic agent at its common or approved dose.

As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a prophylactic or therapeutic agent. Adverse effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a prophylactic or  
15 therapeutic agent might be harmful or uncomfortable or risky. Many are described in the *Physicians' Desk Reference* (56<sup>th</sup> ed. 2002).

As used herein, the term "manage" when used in connection with a disease or condition means to provide beneficial effects to a patient being administered with a prophylactic or therapeutic agent, which does not result in a cure of the disease. In certain  
20 embodiments, a patient is administered with one or more prophylactic or therapeutic agents to manage a disease so as to prevent the progression or worsening of the disease.

As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset of disease-related wasting.

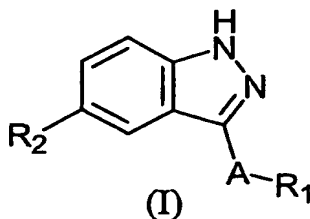
As used herein, the terms "treat" and "treating" include the eradication,  
25 removal, modification, management or control of disease-related wasting.

#### 4. DETAILED DESCRIPTION OF THE INVENTION

##### 4.1 ILLUSTRATIVE JNK INHIBITORS

As mentioned above, the present invention is directed to methods useful for treating or preventing disease-related wasting in a patient, comprising administering an  
30 effective amount of a JNK Inhibitor. Illustrative JNK Inhibitors are set forth below.

In one embodiment, the JNK Inhibitor has the following structure (I):



wherein:

A is a direct bond,  $-(CH_2)_a-$ ,  $-(CH_2)_bCH=CH(CH_2)_c-$ , or  $-(CH_2)_bC\equiv C(CH_2)_c-$ ;

5  $R_1$  is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ ;

$R_2$  is  $-R_3$ ,  $-R_4$ ,  $-(CH_2)_bC(=O)R_5$ ,  $-(CH_2)_bC(=O)OR_5$ ,  $-(CH_2)_bC(=O)NR_5R_6$ ,  
 $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ ,  
 $-(CH_2)_bNR_5C(=O)NR_6R_7$ ,  $-(CH_2)_bNR_5R_6$ ,  $-(CH_2)_bOR_5$ ,

10  $-(CH_2)_bSO_dR_5$  or  $-(CH_2)_bSO_2NR_5R_6$ ;

$a$  is 1, 2, 3, 4, 5 or 6;

$b$  and  $c$  are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

$d$  is at each occurrence 0, 1 or 2;

15  $R_3$  is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl,  $-C(=O)OR_8$ ,  $-OC(=O)R_8$ ,  $-C(=O)NR_8R_9$ ,  $-C(=O)NR_8OR_9$ ,  $-SO_2NR_8R_9$ ,  $-NR_8SO_2R_9$ ,  $-CN$ ,  $-NO_2$ ,  $-NR_8R_9$ ,  $-NR_8C(=O)R_9$ ,  $-NR_8C(=O)(CH_2)_bOR_9$ ,  $-NR_8C(=O)(CH_2)_bR_9$ ,  $-O(CH_2)_bNR_8R_9$ , or heterocycle fused to  
 20 phenyl;

$R_4$  is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ , or  $R_4$  is halogen or hydroxy;

$R_5$ ,  $R_6$  and  $R_7$  are the same or different and at each occurrence independently  
 25 hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of  $R_5$ ,  $R_6$  and  $R_7$  are optionally substituted with one to four substituents independently selected from  $R_3$ ;  
 and

$R_8$  and  $R_9$  are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or  $R_8$  and  $R_9$  taken  
 30 together with the atom or atoms to which they are bonded form a heterocycle, wherein each of  $R_8$ ,  $R_9$ , and  $R_8$  and  $R_9$  taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from  $R_3$ .

In one embodiment,  $-A-R_1$  is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy,  $-NR_8C(=O)R_9$ ,  $-C(=O)NR_8R_9$ ,  
 35 and  $-O(CH_2)_bNR_8R_9$ , wherein  $b$  is 2 or 3 and wherein  $R_8$  and  $R_9$  are defined above.

In another embodiment,  $R_2$  is  $-R_4$ ,  $-(CH_2)_bC(=O)R_5$ ,  $-(CH_2)_bC(=O)OR_5$ ,  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ ,  
 $-(CH_2)_bNR_5C(=O)NR_6R_7$ ,  $-(CH_2)_bNR_5R_6$ ,  $-(CH_2)_bOR_5$ ,  $-(CH_2)_bSO_dR_5$  or  $-(CH_2)_bSO_2NR_5R_6$ , and  $b$  is an integer ranging from 0-4.

5 In another embodiment,  $R_2$  is  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ , 3-triazolyl or 5-tetrazolyl, wherein  $b$  is 0 and wherein  $R_8$  and  $R_9$  are defined above.

In another embodiment,  $R_2$  is 3-triazolyl or 5-tetrazolyl.

In another embodiment:

10 (a)  $-A-R_1$  is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy,  $-NR_8C(=O)R_9$ ,  $-C(=O)NR_8R_9$ , and  $-O(CH_2)_bNR_8R_9$ , wherein  $b$  is 2 or 3; and

(b)  $R_2$  is  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ , 3-triazolyl or 5-tetrazolyl, wherein  $b$  is 0 and wherein  $R_8$  and  $R_9$  are defined above.

In another embodiment:

15 (a)  $-A-R_1$  is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy,  $-NR_8C(=O)R_9$ ,  $-C(=O)NR_8R_9$ , and  $-O(CH_2)_bNR_8R_9$ , wherein  $b$  is 2 or 3; and

(b)  $R_2$  is 3-triazolyl or 5-tetrazolyl.

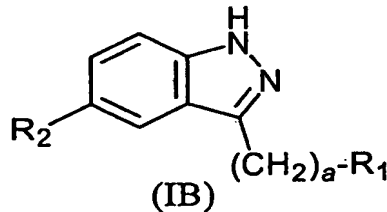
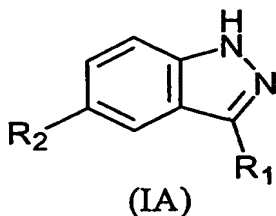
20 In another embodiment,  $R_2$  is  $R_4$ , and  $R_4$  is 3-triazolyl, optionally substituted at its 5-position with:

(a) a  $C_1$ - $C_4$  straight or branched chain alkyl group optionally substituted with a hydroxyl, methylamino, dimethylamino or 1-pyrrolidinyl group; or

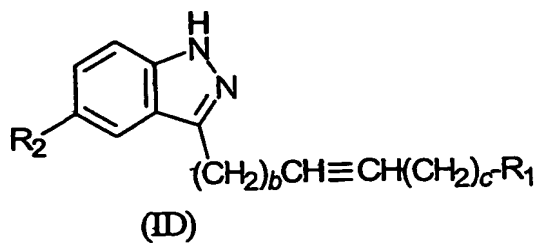
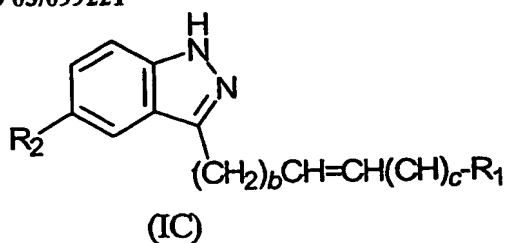
(b) a 2-pyrrolidinyl group.

25 In another embodiment,  $R_2$  is  $R_4$ , and  $R_4$  is 3-triazolyl, optionally substituted at its 5-position with: methyl, n-propyl, isopropyl, 1-hydroxyethyl, 3-hydroxypropyl, methylaminomethyl, dimethylaminomethyl, 1-(dimethylamino)ethyl, 1-pyrrolidinylmethyl or 2-pyrrolidinyl.

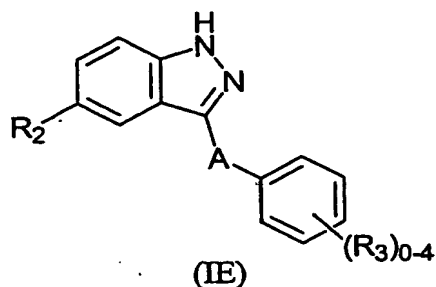
In another embodiment, the compounds of structure (I) have structure (IA) when A is a direct bond, or have structure (IB) when A is  $-(CH_2)_a$ :



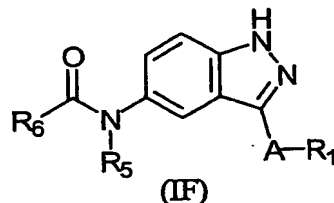
30 In other embodiments, the compounds of structure (I) have structure (IC) when A is a  $-(CH_2)_bCH=CH(CH_2)_c-$ , and have structure (ID) when A is  $-(CH_2)_bC\equiv C(CH_2)_c-$ :



In further embodiments of this invention,  $R_1$  of structure (I) is aryl or substituted aryl, such as phenyl or substituted phenyl as represented by the following structure (IE):



In another embodiment,  $R_2$  of structure (I) is  $-(CH_2)_bNR_4(C=O)R_5$ . In one aspect of this embodiment,  $b=0$  and the compounds have the following structure (IF):

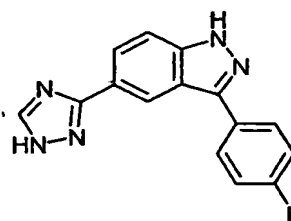


Representative  $R_2$  groups of the compounds of structure (I) include alkyl (such as methyl and ethyl), halo (such as chloro and fluoro), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy and ethoxy), amino, arylalkyloxy (such as benzyloxy), mono- or di-alkylamine (such as  $-NHCH_3$ ,  $-N(CH_3)_2$  and  $-NHCH_2CH_3$ ),  $-NHC(=O)R_4$  wherein  $R_4$  is a substituted or unsubstituted phenyl or heteroaryl (such as phenyl or heteroaryl substituted with hydroxy, carboxy, amino, ester, alkoxy, alkyl, aryl, haloalkyl, halo,  $-CONH_2$  and  $-CONH$  alkyl),  $-NH$ (heteroarylalkyl) (such as  $-NHCH_2$ (3-pyridyl),  $-NHCH_2$ (4-pyridyl), heteroaryl (such as pyrazolo, triazolo and tetrazolo),  $-C(=O)NHR_6$  wherein  $R_6$  is hydrogen, alkyl, or as defined above (such as  $-C(=O)NH_2$ ,  $-C(=O)NHCH_3$ ,  $-C(=O)NH$ (H-carboxyphenyl),  $-C(=O)N(CH_3)_2$ ), arylalkenyl (such as phenylvinyl, 3-nitrophenylvinyl, 4-carboxyphenylvinyl), heteroarylalkenyl (such as 2-pyridylvinyl, 4-pyridylvinyl).

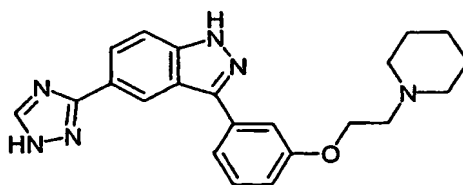
Representative  $R_3$  groups of the compounds of structure (I) include halogen (such as chloro and fluoro), alkyl (such as methyl, ethyl and isopropyl), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy, ethoxy, n-propyloxy and isobutyloxy), amino, mono- or di-alkylamino (such as dimethylamine), aryl (such as phenyl), carboxy, nitro, cyano, sulfinylalkyl (such as methylsulfinyl), sulfonylalkyl (such as methylsulfonyl), sulfonamidoalkyl (such as  $-\text{NHSO}_2\text{CH}_3$ ),  $-\text{NR}_8\text{C}(=\text{O})(\text{CH}_2)_b\text{OR}_9$  (such as  $\text{NHC}(=\text{O})\text{CH}_2\text{OCH}_3$ ),  $\text{NHC}(=\text{O})\text{R}_9$  (such as  $-\text{NHC}(=\text{O})\text{CH}_3$ ,  $-\text{NHC}(=\text{O})\text{CH}_2\text{C}_6\text{H}_5$ ,  $-\text{NHC}(=\text{O})(2\text{-furanyl})$ ), and  $-\text{O}(\text{CH}_2)_b\text{NR}_8\text{R}_9$  (such as  $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ ).

The compounds of structure (I) can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in International Publication No. WO 02/10137 (particularly in Examples 1-430, at page 35, line 1 to page 396, line 12), published February 7, 2002, which is incorporated herein by reference in its entirety. Further, specific examples of these compounds are found in this publication.

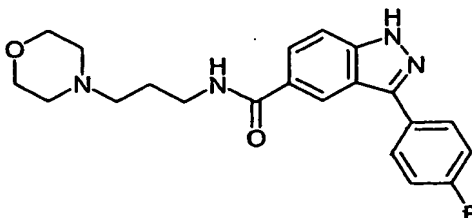
Illustrative examples of JNK Inhibitors of structure (I) are:



3-(4-Fluoro-phenyl)-5-(1H-[1,2,4]triazol-3-yl)-1H-indazole;

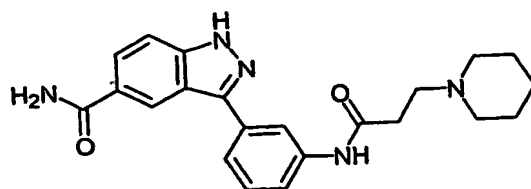


3-[3-(2-Piperidin-1-yl-ethoxy)-phenyl]-5-(1H-[1,2,4]triazol-3-yl)-1H-indazole ;

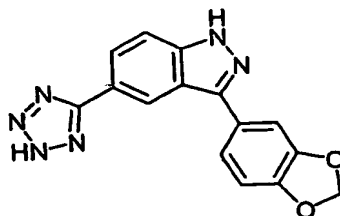


3-(4-Fluoro-phenyl)-1H-indazole-5-carboxylic acid (3-morpholin-4-yl-propyl)-amide ;

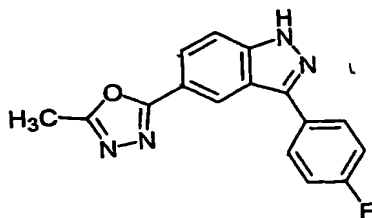
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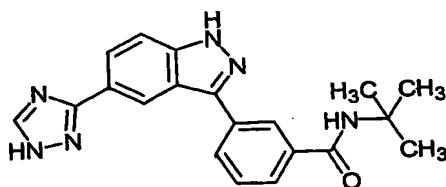
3-[3-(3-Piperidin-1-yl-propionylamino)-phenyl]-1H-indazole-5-carboxylic acid amide ;



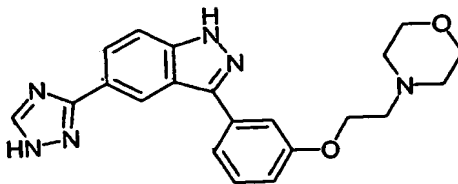
3-Benzo[1,3]dioxol-5-yl-5-(2H-tetrazol-5-yl)-1H-indazole ;



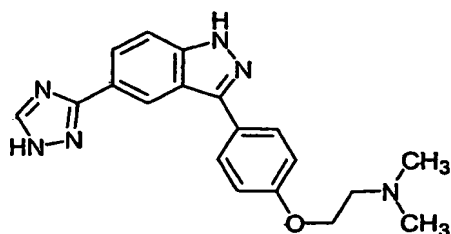
3-(4-Fluoro-phenyl)-5-(5-methyl-[1,3,4]oxadiazol-2-yl)-1H-indazole ;



N-tert-Butyl-3-[5-(1H-[1,2,4]triazol-3-yl)-1H-indazol-3-yl]-benzamide ;

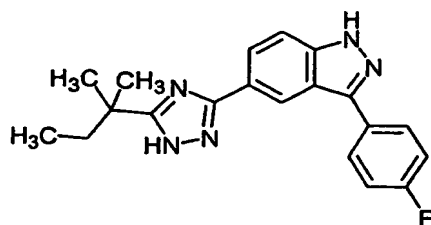


3-[3-(2-Morpholin-4-yl-ethoxy)-phenyl]-5-(1H-[1,2,4]triazol-3-yl)-1H-indazole ;

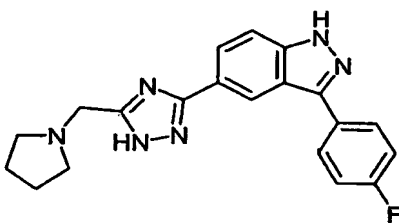


Dimethyl-(2-{4-[5-(1H-[1,2,4]triazol-3-yl)-1H-indazol-3-yl]-phenoxy}-ethyl)-amine ;

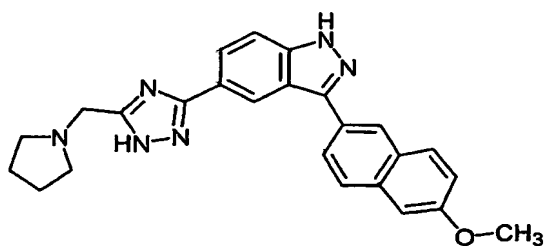
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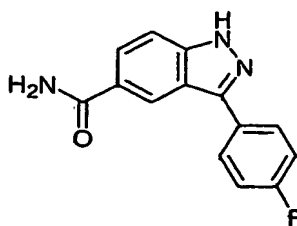
5-[5-(1,1-Dimethyl-propyl)-1H-[1,2,4]triazol-3-yl]-3-(4-fluoro-phenyl)-1H-indazole ;



3-(4-Fluoro-phenyl)-5-(5-pyrrolidin-1-ylmethyl-1H-[1,2,4]triazol-3-yl)-1H-indazole ;



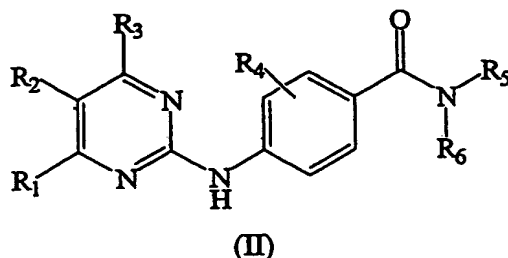
3-(6-Methoxy-naphthalen-2-yl)-5-(5-pyrrolidin-1-ylmethyl-1H-[1,2,4]triazol-3-yl)-1H-indazole ;



3-(4-Fluoro-phenyl)-1H-indazole-5-carboxylic acid amide ;

10 and pharmaceutically acceptable salts thereof.

In another embodiment, the JNK Inhibitor has the following structure (II):



wherein:

R<sub>1</sub> is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R<sub>7</sub>;

R<sub>2</sub> is hydrogen;

R<sub>3</sub> is hydrogen or lower alkyl;

R<sub>4</sub> represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

R<sub>5</sub> and R<sub>6</sub> are the same or different and independently -R<sub>8</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)R<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>(CH<sub>2</sub>)<sub>b</sub>C(=O)R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>C(=O)R<sub>10</sub>, (CH<sub>2</sub>)<sub>a</sub>NR<sub>11</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>SO<sub>c</sub>R<sub>9</sub> or -(CH<sub>2</sub>)<sub>a</sub>SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>;

or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

R<sub>7</sub> is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, substituted heterocycle, heterocycloalkyl, -C(=O)OR<sub>8</sub>, -OC(=O)R<sub>8</sub>, -C(=O)NR<sub>8</sub>R<sub>9</sub>, -C(=O)NR<sub>8</sub>OR<sub>9</sub>, -SO<sub>c</sub>R<sub>8</sub>, -SO<sub>c</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>SO<sub>c</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>C(=O)R<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>OR<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>R<sub>9</sub>, -O(CH<sub>2</sub>)<sub>b</sub>NR<sub>8</sub>R<sub>9</sub>, or heterocycle fused to phenyl;

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;

or R<sub>8</sub> and R<sub>9</sub> taken together with the atom or atoms to which they are attached to form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

5 In one embodiment,  $R_1$  is a substituted or unsubstituted aryl or heteroaryl. When  $R_1$  is substituted, it is substituted with one or more substituents defined below. In one embodiment, when substituted,  $R_1$  is substituted with a halogen,  $-SO_2R_8$  or  $-SO_2R_8R_9$ .

In another embodiment,  $R_1$  is substituted or unsubstituted aryl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl or quinazolinyl.

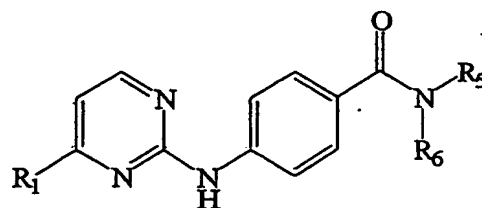
In another embodiment  $R_1$  is substituted or unsubstituted aryl or heteroaryl. When  $R_1$  is substituted, it is substituted with one or more substituents defined below. In one embodiment, when substituted,  $R_1$  is substituted with a halogen,  $-SO_2R_8$  or  $-SO_2R_8R_9$ .

In another embodiment,  $R_1$  is substituted or unsubstituted aryl, preferably phenyl. When  $R_1$  is a substituted aryl, the substituents are defined below. In one embodiment, when substituted,  $R_1$  is substituted with a halogen,  $-SO_2R_8$  or  $-SO_2R_8R_9$ .

In another embodiment,  $R_5$  and  $R_6$ , taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted nitrogen-containing non-aromatic heterocycle, in one embodiment, piperazinyl, piperidinyl or morpholinyl.

When  $R_5$  and  $R_6$ , taken together with the nitrogen atom to which they are attached form substituted piperazinyl, piperadinyl or morpholinyl, the piperazinyl, piperadinyl or morpholinyl is substituted with one or more substituents defined below. In one embodiment, when substituted, the substituent is alkyl, amino, alkylamino, alkoxyalkyl, acyl, pyrrolidinyl or piperidinyl.

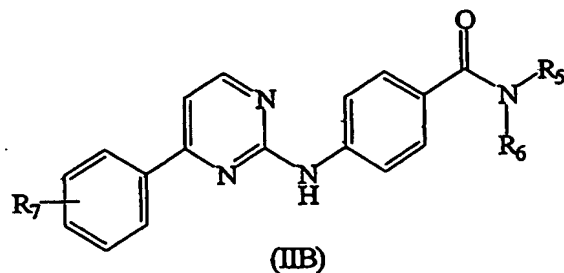
In one embodiment,  $R_3$  is hydrogen and  $R_4$  is not present, and the JNK Inhibitor has the following structure (IIA):



(IIA)

and pharmaceutically acceptable salts thereof.

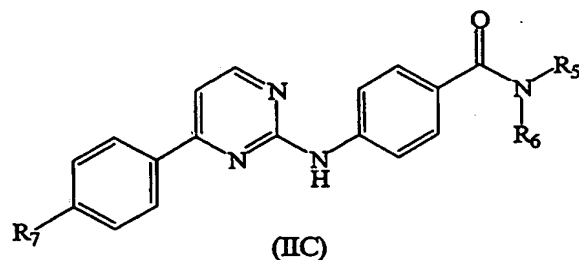
In a more specific embodiment,  $R_1$  is phenyl optionally substituted with  $R_7$ , and having the following structure (IIB):



5

and pharmaceutically acceptable salts thereof.

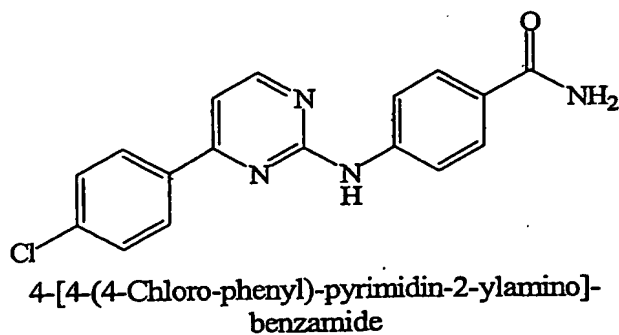
In still a further embodiment,  $R_7$  is at the para position of the phenyl group relative to the pyrimidine, as represented by the following structure (IIC):

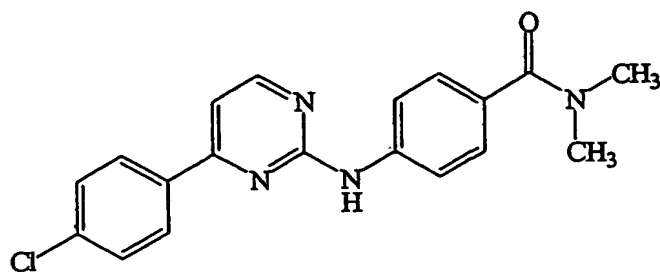


10 and pharmaceutically acceptable salts thereof.

The JNK Inhibitors of structure (II) can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in International Publication No. WO 02/46170 (particularly Examples 1-27 at page 23, line 5 to page 183, line 25), published June 13, 2002, which is hereby incorporated by reference in  
15 its entirety. Further, specific examples of these compounds are found in the publication.

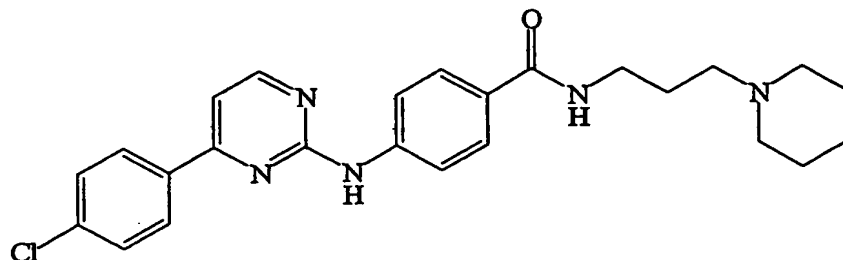
Illustrative examples of JNK Inhibitors of structure (II) are:



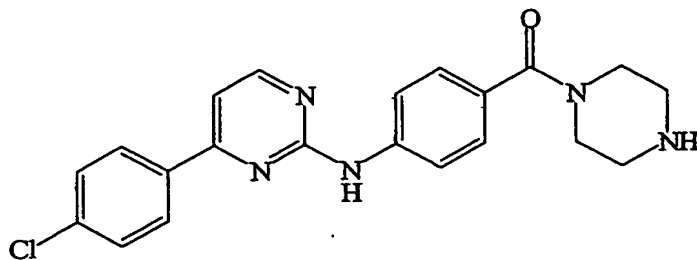


4-[4-(4-Chloro-phenyl)-pyrimidin-2-ylamino]-*N,N*-dimethylbenzamide ;

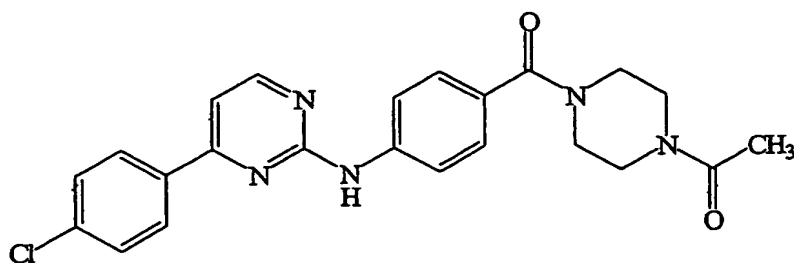
5



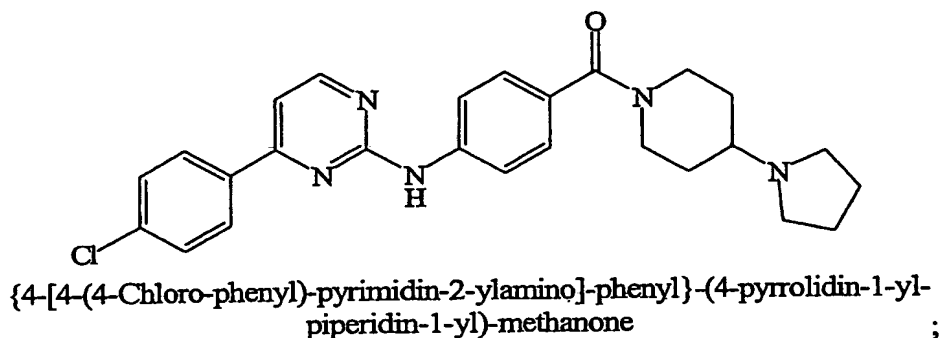
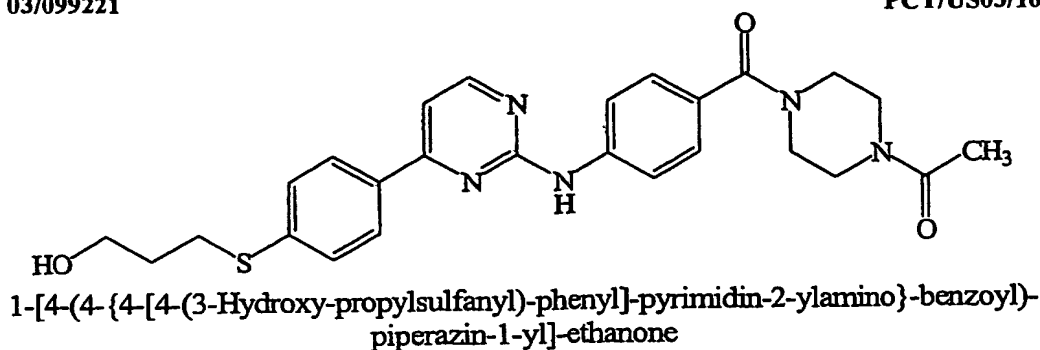
4-[4-(4-Chloro-phenyl)-pyrimidin-2-ylamino]-*N*-(3-piperidin-1-yl-propyl)benzamide ;



{4-[4-(4-Chloro-phenyl)-pyrimidin-2-ylamino]-phenyl}-piperazin-1-yl-methanone ;

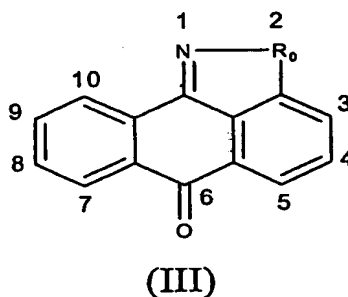


1-(4-{4-[4-(4-Chloro-phenyl)-pyrimidin-2-ylamino]-benzoyl}-piperazin-1-yl)-ethanone ;



and pharmaceutically acceptable salts thereof.

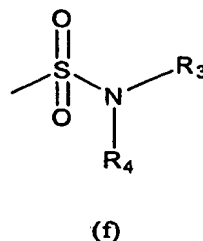
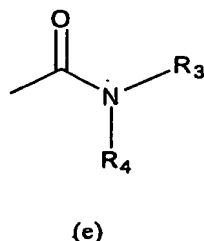
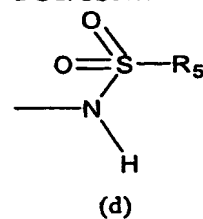
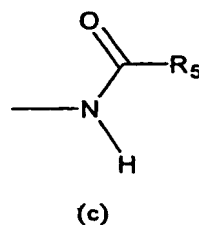
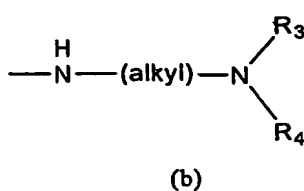
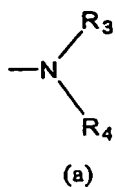
In another embodiment, the JNK Inhibitor has the following structure (III):



wherein  $R_0$  is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, NH or -CH<sub>2</sub>-;

the compound of structure (III) being: (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

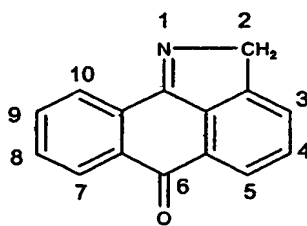
the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position, wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



wherein  $R_3$  and  $R_4$  are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

$R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

In another embodiment, the JNK Inhibitor has the following structure (IIIA):



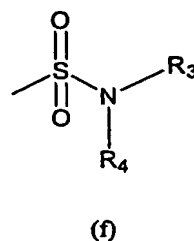
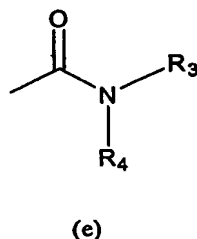
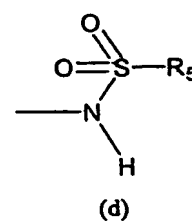
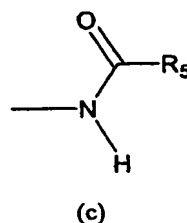
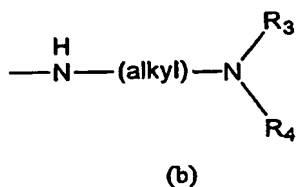
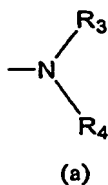
2H-Dibenzo[cd,g]indol-6-one  
(IIIA)

being: (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl,

- 5 alkoxyalkoxy, aminoalkoxy, mono- alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



- wherein R<sub>3</sub> and R<sub>4</sub> are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

- R<sub>5</sub> is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

A subclass of the compounds of structure (IIIA) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

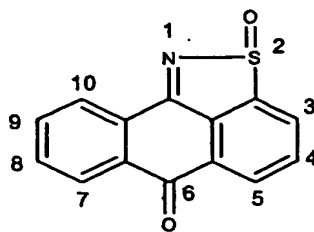
- A second subclass of compounds of structure (IIIA) is that wherein the first or second substituent is present at the 5, 7, or 9 position;

the first or second substituent is independently alkoxy, aryloxy, aminoalkyl, mono-alkylaminoalkyl, di-alkylaminoalkyl, or a group represented by the structure (a), (c), (d), (e), or (f);

- R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

R<sub>5</sub> is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

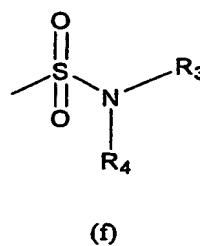
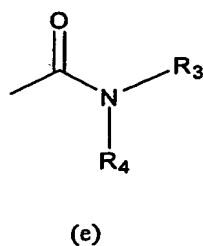
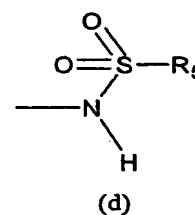
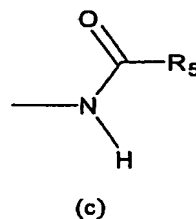
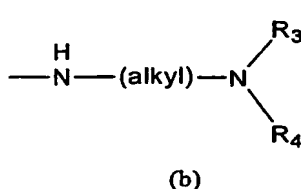
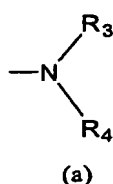
In another embodiment, the JNK Inhibitor has the following structure (IIIB):



2-Oxo-2H-21<sup>4</sup>-anthra[9,1-cd]  
isothiazol-6-one  
(IIIB)

being (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (ii) disubstituted and having a first substituent and a second substituent; the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b) (c), (d), (e), or (f):



wherein R<sub>3</sub> and R<sub>4</sub> are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

R<sub>5</sub> is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino,

5 arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

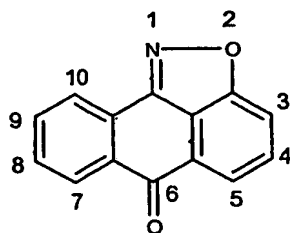
A subclass of the compounds of structure (IIIB) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

10 A second subclass of the compounds of structure (IIIB) is that wherein the first or second substituent is independently alkoxy, aryloxy, or a group represented by the structure (a), (c), (d), (e), or (f);

$R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

15  $R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

In another embodiment, the JNK Inhibitor has the following structure (IIIC):

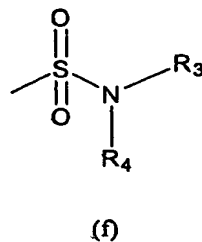
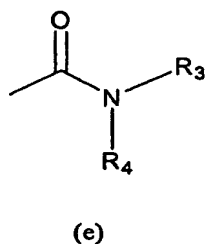
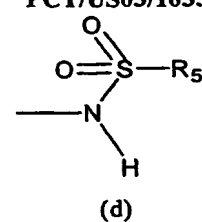
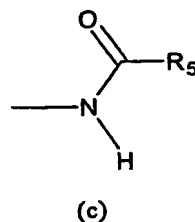
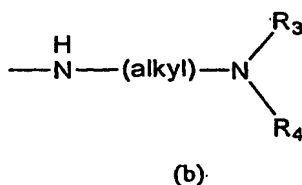
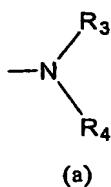


2-Oxa-1-aza-aceanthrylen-6-one  
(IIIC)

being (i) monosubstituted and having a first substituent or (ii) disubstituted and having a first substituent and a second substituent;

20 the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, 25 alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c) (d), (e), or (f):



5

wherein  $R_3$  and  $R_4$  are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

10

$R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

15

A subclass of the compounds of structure (IIC) is that wherein the first or second substituent is present at the 5, 7, or 9 position. In one embodiment, the first or second substituent is present at the 5 or 7 position.

A second subclass of the compounds of structure (IIC) is that wherein the first or second substituent is independently alkoxy, aryloxy, aminoalkyl, mono-alkylaminoalkyl, di-alkylaminoalkyl, or a group represented by the structure (a), (c), (d), (e), or (f);

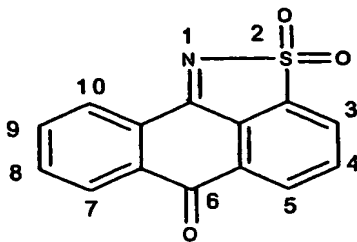
20

$R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

$R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl.

25

In another embodiment, the JNK Inhibitor has the following structure (IIID):



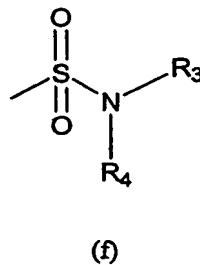
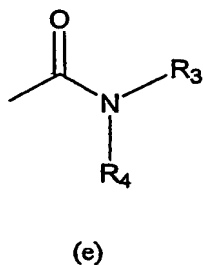
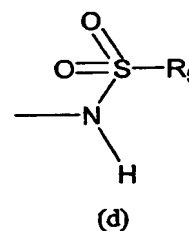
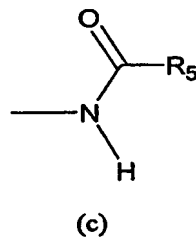
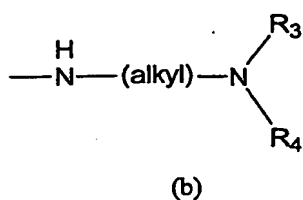
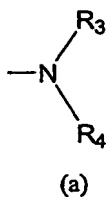
2,2-Dioxo-2H-21<sup>6</sup>-anthra  
[9,1-cd]isothiazol-6-one  
(IIID)

5

being (i) monosubstituted and having a first substituent present at the 5, 7, or 9 position, (ii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 7 position, (iii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 9 position, or (iv)

10 disubstituted and having a first substituent present at the 7 position and a second substituent present at the 9 position;

wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, 15 alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



wherein R<sub>3</sub> and R<sub>4</sub> are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R<sub>3</sub> and R<sub>4</sub> are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono- 20 alkylaminoalkyl, or di-alkylaminoalkyl; and

5  $R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

10 A subclass of the compounds of structure (IIID) is that wherein the first or second substituent is present at the 5 or 7 position.

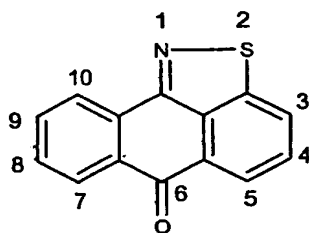
A second subclass of the compounds of structure (IIID) is that wherein the first or second substituent is independently alkyl, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (c), (d), (e), or (f).

Another subclass of the compounds of structure (IIID) is that wherein the first and second substituent are independently alkoxy, aryloxy, or a group represented by the structure (a), (c), (d), (e), or (f);

20  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, or cycloalkylalkyl; and

$R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, alkoxycarbonyl, or cycloalkylalkyl.

In another embodiment, the JNK Inhibitor has the following structure (IIIE):

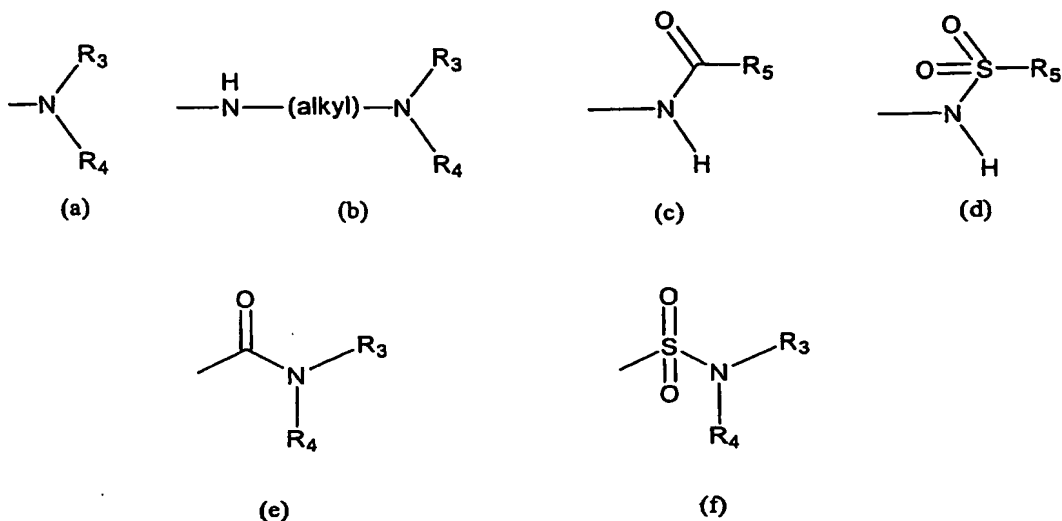


Anthra[9,1-*cd*]isothiazol-6-one  
(IIIE)

25 being (i) monosubstituted and having a first substituent present at the 5, 7, or 9 position, (ii) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 9 position, (iii) disubstituted and having a first substituent present at the 7 position and a second substituent present at the 9 position, or (iv) disubstituted and having a first substituent present at the 5 position and a second substituent present at the 7 position;

30 wherein the first and second substituent, when present, are independently alkyl, halogen, hydroxy, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl,

- 5 alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



- wherein  $R_3$  and  $R_4$  are taken together and represent alkylidene or a  
 10 heteroatom-containing cyclic alkylidene or  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

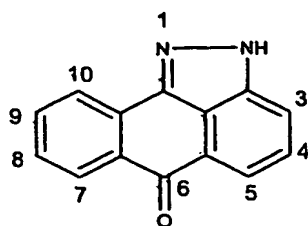
- $R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino,  
 15 arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

A subclass of the compounds of structure (III E) is that wherein the first or second substituent is present at the 5 or 7 position.

- A second subclass of the compounds of structure (III E) is that wherein the  
 20 compound of structure (III E) is disubstituted and at least one of the substituents is a group represented by the structure (d) or (f).

- Another subclass of the compounds of structure (III E) is that wherein the compounds are monosubstituted. Yet another subclass of compounds is that wherein the compounds are monosubstituted at the 5 or 7 position with a group represented by the  
 25 structure (e) or (f).

In another embodiment, the JNK Inhibitor has the following structure (III F):

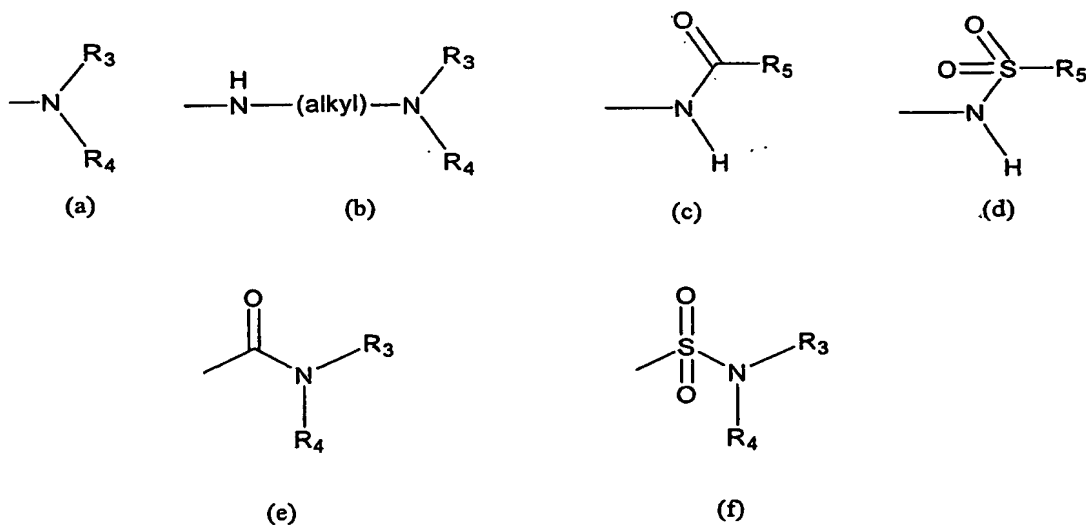


2H-Dibenzo[cd,g]indazol-6-one  
(IIIF)

being (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position;

wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by structure (a), (b), (c), (d), (e), or (f):



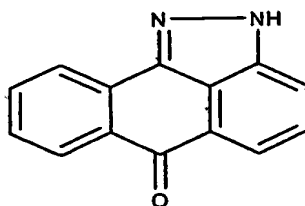
wherein  $R_3$  and  $R_4$  are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

$R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

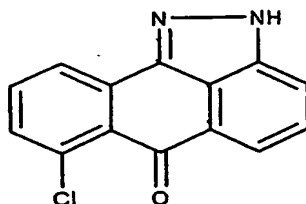
5 In one embodiment, the compound of structure (III<sup>F</sup>), or a pharmaceutically acceptable salt thereof is unsubstituted at the 3, 4, 5, 7, 8, 9, or 10 position.

The JNK Inhibitors of structure (III) can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in International Publication No. WO 01/12609 (particularly Examples 1-7 at page 24, line 6 to  
10 page 49, line 16), published February 22, 2001, as well as International Publication No. WO 02/066450 (particularly compounds AA-HG at pages 59-108), published August 29, 2002, each of which is hereby incorporated by reference in its entirety. Further, specific examples of these compounds can be found in the publications.

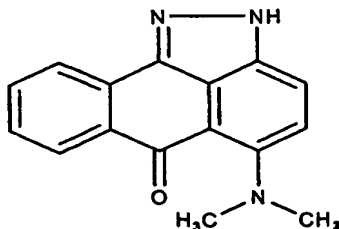
Illustrative examples of JNK Inhibitors of structure (III) are:



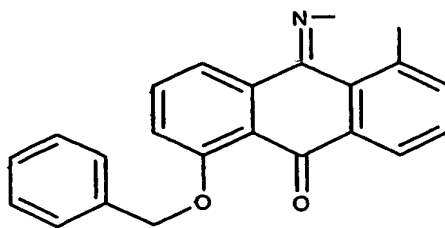
15 2H-Dibenzo[cd,g]  
indazol-6-one ;



7-Chloro-2H-dibenzo[cd,g]  
indazol-6-one ;

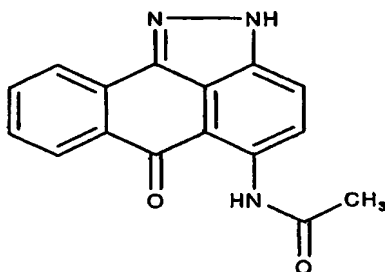


5-Dimethylamino-2H-  
dibenzo[cd,g]indazol-6-one;

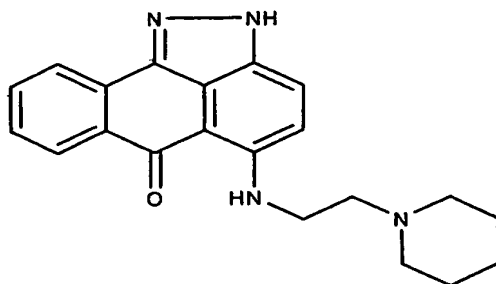


7-Benzyloxy-2*H*-dibenzo[*cd,g*]indazol-6-one ;

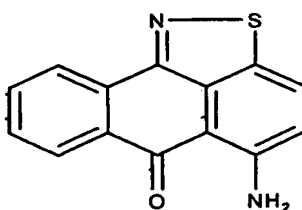
5



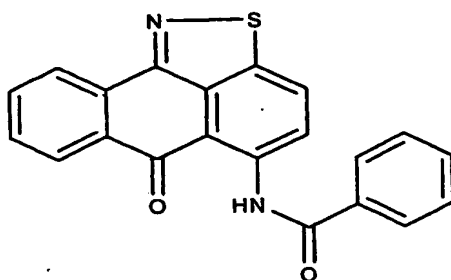
N-(6-Oxo-2,6-dihydro-dibenzo[*cd,g*]indazol-5-yl)-acetamide ;



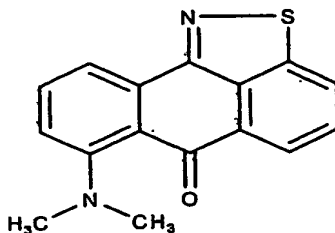
5-(2-Piperidin-1-yl-ethylamino)-2*H*-dibenzo[*cd,g*]indazol-6-one ;



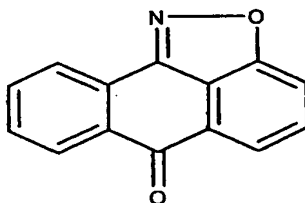
5-Amino-anthra[9,1-*cd*]isothiazol-6-one ;



5 *N*-(6-Oxo-6*H*-anthra[9,1-*cd*]isothiazol-5-yl)-benzamide ;



7-Dimethylamino-anthra[9,1-*cd*]isothiazol-6-one ;



2-Oxa-1-aza-aceanthrylen-6-one;

and pharmaceutically acceptable salts thereof.

Other JNK Inhibitors that are useful in the present methods include, but are not limited to, those disclosed in International Publication No. WO 00/39101, (particularly at page 2, line 10 to page 6, line 12); International Publication No. WO 01/14375 (particularly at page 2, line 4 to page 4, line 4); International Publication No. WO 00/56738 (particularly at page 3, line 25 to page 6, line 13); International Publication No. WO 01/27089 (particularly at page 3, line 7 to page 5, line 29); International Publication No. WO 00/12468 (particularly at page 2, line 10 to page 4, line 14); European Patent Publication 1 110 957 (particularly at page 19, line 52 to page 21, line 9); International Publication No. WO 00/75118 (particularly at page 8, line 10 to page 11, line 26); International Publication No. WO 01/12621 (particularly at page 8, line 10 to page 10, line 7); International Publication No. WO 00/64872 (particularly at page 9, line 1 to page, 106, line 2); International Publication No. WO 01/23378 (particularly at page 90, line 1 to page 91, line 11); International Publication No. WO 02/16359 (particularly at page 163, line 1 to

5 page 164, line 25); United States Patent No. 6,288,089 (particularly at column 22, line 25 to column 25, line 35); United States Patent No. 6,307,056 (particularly at column 63, line 29 to column 66, line 12); International Publication No. WO 00/35921 (particularly at page 23, line 5 to page 26, line 14); International Publication No. WO 01/91749 (particularly at page 29, lines 1-22); International Publication No. WO 01/56993 (particularly in at page 43 to  
10 page 45); and International Publication No. WO 01/58448 (particularly in at page 39), each of which is incorporated by reference herein in its entirety.

Pharmaceutical compositions including dosage forms of the invention, which comprise an effective amount of a JNK Inhibitor can be used in the methods of the invention.

#### 15 4.2 METHODS OF USE

The present invention provides methods useful for treating or preventing disease-related wasting in a patient comprising administering an effective amount of a JNK Inhibitor.

In one embodiment, the disease is HIV.

20 In another embodiment, the disease is AIDS.

In another embodiment, the disease is cancer.

In another embodiment, the disease is end-stage renal disease.

In another embodiment, the disease is kidney failure.

In another embodiment, the disease is chronic heart disease.

25 In another embodiment, the disease is obstructive pulmonary disease.

In another embodiment, the disease is tuberculosis.

In another embodiment, the disease is rheumatoid arthritis.

In another embodiment, the disease is a chronic inflammatory disease including, but not limited to, scleroderma and mixed connective tissue disease.

30 In another embodiment, the disease is a chronic infectious disease including, but not limited to, osteoarthritis and bacterial endocarditis.

The present invention also provides methods useful for treating or preventing disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor and a prophylactic or therapeutic agent.

35 In one embodiment, the prophylactic or therapeutic agent is useful for the treatment or prevention of HIV or AIDS. Agents useful for treating or preventing HIV or AIDS include, but are not limited to, amprenavir (sold as a formulation under the trade name AGNERASE); nelfinavir (sold as a formulation under the trade name VIRACEPT);

5 saquinavir (sold as a formulation under the trade name FORTOVASE); indinavir (sold as a formulation under the trade name CRIVAN); saquinavir (sold as a formulation under the trade name INVIRASE); lopinavir (sold as a formulation under the trade name KALETRA); ritonavir (sold as a formulation under the trade name NORVIR); or GW433908. In other certain embodiments, the AIDS therapeutic agent is a reverse transcriptase inhibitor  
10 including, but not limited to: 3TC / lamivudine (sold as a formulation under the trade name EPIVIR); ddC / zalcitabine (sold as a formulation under the trade name HIVID); delavirdine (sold as a formulation under the trade name RESCRIPTOR); zidovudine (sold as a formulation under the trade name RETROVIR); efavirenz (sold as a formulation under the trade name SUSTIVA); a combination of abacavir, zidovudine and lamivudine (sold as a formulation under the trade name TRIZIVIR); ddI / didanosine (sold as a formulation under the trade name VIDEX); nevirapine (sold as a formulation under the trade name VIRAMUNE); tenofovir disoproxil fumarate (sold as a formulation under the trade name VIREAD); d4T / stavudine (sold as a formulation under the trade name ZERIT); or abacavir (sold as a formulation under the trade name ZIAGEN).

20 In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of end-stage renal disease. Agents or methods useful for treating or preventing end-stage renal disease include, but are not limited to, angiotensin II, cisplatin, dialysis or lisinopril.

25 In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of kidney failure. Agents or methods useful for treating or preventing kidney failure include, but are not limited to, angiotensin II, cisplatin, dialysis or lisinopril.

30 In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of chronic heart disease. Agents useful for treating or preventing chronic heart disease include, but are not limited to, perindopril.

In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of obstructive pulmonary disease. Agents useful for treating or preventing obstructive pulmonary disease include, but are not limited to, such as budesonide, prednisolone, beta(2)-agonists, ipratropium bromide or oral antibiotics.

35 In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of cancer. Agents useful for treating or preventing cancer include, but are not limited to, aciclovir, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin,

5 batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropiramine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, 10 decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbitux, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, 15 etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1 , interferon alfa-n3, interferon beta-I 20 a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, cantansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedpa, mitindomide, mitocarcin, mitocromin, mitogillin, 25 mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, 30 rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, 35 trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

5 Other anti-cancer drugs include, but are not limited to, 20-epi-1,25  
dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol;  
adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox;  
amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole;  
andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-  
10 dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen;  
antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene  
modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase;  
asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron;  
azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists;  
15 benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin  
B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine;  
bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine;  
calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine;  
carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage  
20 derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B;  
cetorelix; chlorlins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine;  
clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4;  
combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;  
cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatam; cypemycin;  
25 cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin  
B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone;  
didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-;  
dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine;  
droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab;  
30 eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen  
agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole;  
fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;  
fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin;  
fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase  
35 inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene  
bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine;  
ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth  
factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane;  
iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B;

- 5 itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin;
- 10 loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin
- 15 fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip;
- 20 naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives;
- 25 palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-
- 30 triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras
- 35 farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohikutine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single

5 chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic  
10 glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene  
15 bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; tricinibine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine;  
20 vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of tuberculosis. Agents useful for treating or preventing tuberculosis include, but are not limited to, infliximab, rifampicin or streptomycin.

In other embodiments, the prophylactic or therapeutic agent is useful for the  
25 treatment or prevention of rheumatoid arthritis. Agents useful for treating or preventing rheumatoid arthritis include, but are not limited to, hydroxychloroquine, NSAIDs (*e.g.*, aspirin, ibuprofen and naproxen), arava, enbrel, remicade, kineret, azulfidene and aralen.

In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of chronic inflammatory disease including, but not limited to,  
30 scleroderma and mixed connective tissue disease. Agents useful for treating or preventing a chronic inflammatory disease include, but are not limited to, NSAIDs (*e.g.*, aspirin, ibuprofen and naproxen), arava, enbrel, remicade, kineret, azulfidene and aralen.

In other embodiments, the prophylactic or therapeutic agent is useful for the treatment or prevention of a chronic infectious disease including, but not limited to,  
35 osteoarthritis and bacterial endocarditis. Agents useful for treating or preventing a chronic infectious disease include, but are not limited to, acetaminophen and NSAIDs (*e.g.*, aspirin, ibuprofen and naproxen).

5           In another embodiment, the disease-related wasting is associated with a weight loss of greater than about 5% of baseline body weight, which is optionally accompanied by chronic diarrhea, chronic weakness or fever.

          The methods and compositions of the invention are useful not only in untreated patients but are also useful in the treatment of patients partially or completely  
10   refractory to current standard and experimental disease-related wasting therapy, including but not limited to appetite stimulants, hormonal therapy, and/or biological therapy/immunotherapy.

          Further, the methods of the invention allow the treatment of disease-related wasting using lower and/or less frequent doses of appetite stimulants, hormonal therapy,  
15   and/or biological therapy/immunotherapy to reduce the incidence of unwanted or adverse effects caused by administration of current/conventional agents while maintaining or enhancing the efficacy of treatment. In other embodiments of the invention, lower and/or less frequent doses of a JNK Inhibitor can be used for the treatment and/or prevention of disease-related wasting.

20           In one embodiment, a JNK Inhibitor and a prophylactic or therapeutic agent are administered to an animal, preferably a mammal, more preferably a human, in a sequence and within a time interval such that the JNK Inhibitor can act together with the other agent to provide an increased benefit than if they were administered otherwise. For example, each prophylactic or therapeutic agent can be administered at the same time or  
25   sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In one embodiment, the JNK Inhibitor and the prophylactic or therapeutic agent exert their effect at times which overlap. Each prophylactic or therapeutic agent can be administered separately, in any appropriate form  
30   and by any suitable route. In other embodiments, the JNK Inhibitor is administered before, concurrently or after administration of the therapeutic or prophylactic agent. Surgery can also be performed as a preventive measure or to relieve pain.

          In various embodiments, the JNK Inhibitor and prophylactic or therapeutic agent are administered less than about 1 hour apart, at about 1 hour apart, at about 1 hour to  
35   about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart

5 or no more than 48 hours apart. In other embodiments, the JNK Inhibitor and prophylactic or therapeutic agent are administered concurrently.

In other embodiments, the JNK Inhibitor and prophylactic or therapeutic agent is administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week part, at about 1 to 2 weeks apart, or more than 2 weeks apart. In preferred embodiments, the  
10 prophylactic or therapeutic agents are administered in a time frame where both agents are still active. One skilled in the art would be able to determine such a time frame by determining the half life of the administered agents.

In certain embodiments, the JNK Inhibitor and optionally the prophylactic or therapeutic agent are cyclically administered to a patient. Cycling therapy involves the  
15 administration of a first agent for a period of time, followed by the administration of a second agent and/or third agent for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improve the efficacy of the treatment.

20 In certain embodiments, the JNK Inhibitor and optionally the prophylactic or therapeutic agent are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of a JNK Inhibitor and optionally the therapeutic or prophylactic agent by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes  
25 every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

In yet other embodiments, the JNK Inhibitor is administered in metronomic  
30 dosing regimens, either by continuous infusion or frequent administration without extended rest periods. Such metronomic administration can involve dosing at constant intervals without rest periods. Typically the JNK Inhibitors, are used at lower doses. Such dosing regimens encompass the chronic daily administration of relatively low doses for extended periods of time. In preferred embodiments, the use of lower doses can minimize toxic side  
35 effects and eliminate rest periods. In certain embodiments, the JNK Inhibitor is delivered by chronic low-dose or continuous infusion ranging from about 24 hours to about 2 days, to about 1 week, to about 2 weeks, to about 3 weeks to about 1 month to about 2 months, to about 3 months, to about 4 months, to about 5 months, to about 6 months. The scheduling of such dose regimens can be optimized by the skilled artisan.

5           In other embodiments, courses of treatment are administered concurrently to a patient, *i.e.*, individual doses of the therapeutic or prophylactic agent are administered separately yet within a time interval such that the JNK Inhibitor can work together with the therapeutic or prophylactic agent. For example, one component can be administered once per week in combination with the other components that can be administered once every  
10 two weeks or once every three weeks. In other words, the dosing regimens are carried out concurrently even if the therapeutics are not administered simultaneously or during the same day.

          The prophylactic and/or therapeutic agent can act additively or, more preferably, synergistically with the JNK Inhibitor. In one embodiment, a JNK Inhibitor is  
15 administered concurrently with one or more therapeutic or prophylactic agents in the same pharmaceutical composition. In another embodiment, a JNK Inhibitor is administered concurrently with one or more therapeutic or prophylactic agents in separate pharmaceutical compositions. In still another embodiment, a JNK Inhibitor is administered prior to or subsequent to administration of a therapeutic or prophylactic agent. The invention  
20 contemplates administration of a JNK Inhibitor and a prophylactic or therapeutic agent by the same or different routes of administration, *e.g.*, oral and parenteral. In certain embodiments, when a JNK Inhibitor is administered concurrently with a prophylactic or therapeutic agent that potentially produces adverse side effects including, but not limited to, toxicity, the prophylactic or therapeutic agent can advantageously be administered at a dose  
25 that falls below the threshold that the adverse side effect is elicited.

#### 4.3    PHARMACEUTICAL COMPOSITIONS

          The compositions comprising a JNK Inhibitor include bulk-drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, impure or non-sterile compositions) and pharmaceutical compositions (*i.e.*, compositions that are  
30 suitable for administration to a patient) which can be used in the preparation of unit dosage forms. Such compositions optionally comprise a prophylactically or therapeutically effective amount of a prophylactic and/or therapeutic agent disclosed herein or a combination of those agents and a pharmaceutically acceptable carrier. Preferably, compositions of the invention comprise a prophylactically or therapeutically effective  
35 amount of JNK Inhibitor and another therapeutic or prophylactic agent, and a pharmaceutically acceptable carrier.

          In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S.

5 Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which a JNK Inhibitor is administered. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical  
10 vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used. When administered to a patient, the pharmaceutically acceptable vehicles are preferably sterile. Water can be the vehicle when the JNK Inhibitor is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be  
15 employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propyleneglycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.  
20

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a  
25 capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

In a preferred embodiment, the JNK Inhibitor and optionally the a therapeutic or prophylactic agent are formulated in accordance with routine procedures as pharmaceutical compositions adapted for intravenous administration to human beings.  
30 Typically, JNK Inhibitors for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized  
35 powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the JNK Inhibitor is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the JNK Inhibitor is

5 administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more optional agents, for  
10 example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively  
15 permeable membranes surrounding an osmotically active driving compound are also suitable for an orally administered JNK Inhibitor. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of  
20 immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. Such vehicles are preferably of pharmaceutical grade.

Further, the effect of the JNK Inhibitor can be delayed or prolonged by  
25 proper formulation. For example, a slowly soluble pellet of the JNK Inhibitor can be prepared and incorporated in a tablet or capsule. The technique can be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules can be coated with a film which resists dissolution for a predictable period of time. Even the parenteral preparations can be made long-acting, by dissolving or  
30 suspending the compound in oily or emulsified vehicles which allow it to disperse only slowly in the serum.

#### 4.4 FORMULATIONS

35 Pharmaceutical compositions for use in accordance with the present invention can be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

5           Thus, the JNK Inhibitor and optionally the therapeutic or prophylactic agent and their physiologically acceptable salts and solvates can be formulated into pharmaceutical compositions for administration by inhalation or insufflation (either through the mouth or the nose) or oral, parenteral or mucosal (such as buccal, vaginal, rectal, sublingual) administration. In one embodiment, local or systemic parenteral administration is used.

10           For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

25           Preparations for oral administration can be suitably formulated to give controlled release of the active compound.

30           For buccal administration the pharmaceutical compositions can take the form of tablets or lozenges formulated in conventional manner.

35           For administration by inhalation, the pharmaceutical compositions for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

5           The pharmaceutical compositions can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain  
10   formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

          The pharmaceutical compositions can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional  
15   suppository bases such as cocoa butter or other glycerides.

          In addition to the formulations described previously, the pharmaceutical compositions can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the pharmaceutical compositions can be  
20   formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

          The invention also provides that a pharmaceutical composition is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity. In  
25   one embodiment, the pharmaceutical composition is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a patient.

          In other embodiments of the invention, radiation therapy agents such as  
30   radioactive isotopes can be given orally as liquids in capsules or as a drink. Radioactive isotopes can also be formulated for intravenous injection. The skilled oncologist can determine the preferred formulation and route of administration.

          The pharmaceutical compositions can, if desired, be presented in a pack or dispenser device that can contain one or more unit dosage forms containing the active  
35   ingredient. The pack can for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration.

          In certain preferred embodiments, the pack or dispenser contains one or more unit dosage forms containing no more than the recommended dosage formulation as

5 determined in the *Physician's Desk Reference* (56<sup>th</sup> ed. 2002, herein incorporated by reference in its entirety).

#### 4.5 ROUTES OF ADMINISTRATION

Methods of administering a JNK Inhibitor and optionally a therapeutic or prophylactic agent include, but are not limited to, parenteral administration (*e.g.*,  
10 intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal, rectal, vaginal, sublingual, buccal or oral routes). In a specific embodiment, the JNK Inhibitor and optionally the prophylactic or therapeutic agents are administered intramuscularly, intravenously, or subcutaneously. The JNK Inhibitor and optionally the prophylactic or therapeutic agent can also be administered by infusion or  
15 bolus injection and can be administered together with other biologically active agents. Administration can be local or systemic. The JNK Inhibitor and optionally the prophylactic or therapeutic agent and their physiologically acceptable salts and solvates can also be administered by inhalation or insufflation (either through the mouth or the nose). In a preferred embodiment, local or systemic parenteral administration is used.

20 In specific embodiments, it can be desirable to administer the JNK Inhibitor locally to the area in need of treatment. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or  
25 gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of an atherosclerotic plaque tissue.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or  
30 synthetic pulmonary surfactant. In certain embodiments, the JNK Inhibitor can be formulated as a suppository, with traditional binders and vehicles such as triglycerides.

In another embodiment, the JNK Inhibitor can be delivered in a vesicle, in particular a liposome (*see* Langer, 1990, *Science* 249:1527-1533; Treat *et al.*, in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; *see generally ibid.*).  
35

In yet another embodiment, the JNK Inhibitor can be delivered in a controlled release system. In one embodiment, a pump can be used (*see* Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald *et al.*, 1980, *Surgery* 88:507

5 Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used (*see* Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; *see also* Levy *et al.*, 10 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 71:105). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the JNK Inhibitor, *e.g.*, the liver, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in 15 the review by Langer, 1990, *Science* 249:1527-1533) can be used.

#### 4.6 DOSAGES

The amount of the JNK Inhibitor that is effective in the treatment or prevention of disease-related wasting can be determined by standard research techniques. For example, the dosage of the JNK Inhibitor which will be effective in the treatment or 20 prevention of disease-related wasting can be determined by administering the JNK Inhibitor to an animal in a model such as, *e.g.*, the animal models known to those skilled in the art. In addition, *in vitro* assays can optionally be employed to help identify optimal dosage ranges.

Selection of a particular effective dose can be determined (*e.g.*, via clinical trials) by a skilled artisan based upon the consideration of several factors which will be 25 known to one skilled in the art. Such factors include the disease to be treated or prevented, the symptoms involved, the patient's body mass, the patient's immune status and other factors known by the skilled artisan.

The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease-related wasting, and should be 30 decided according to the judgment of the practitioner and each patient's circumstances. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The dose of a JNK Inhibitor to be administered to a patient, such as a human, is rather widely variable and can be subject to independent judgment. It is often practical to 35 administer the daily dose of a JNK Inhibitor at various hours of the day. However, in any given case, the amount of a JNK Inhibitor administered will depend on such factors as the solubility of the active component, the formulation used, patient condition (such as weight), and/or the route of administration.

5           The general range of effective amounts of the JNK Inhibitor alone or in combination with the prophylactic or therapeutic agent(s) are from about 0.001 mg/day to about 1000 mg/day, more preferably from about 0.001 mg/day to 750 mg/day, more preferably from about 0.001 mg/day to 500 mg/day, more preferably from about 0.001 mg/day to 250 mg/day, more preferably from about 0.001 mg/day to 100 mg/day, more preferably from about 0.001 mg/day to 75 mg/day, more preferably from about 0.001 mg/day to 50 mg/day, more preferably from about 0.001 mg/day to 25 mg/day, more preferably from about 0.001 mg/day to 10 mg/day, more preferably from about 0.001 mg/day to 1 mg/day. Of course, it is often practical to administer the daily dose of compound in portions, at various hours of the day. However, in any given case, the amount of compound administered will depend on such factors as the solubility of the active component, the formulation used, subject condition (such as weight), and/or the route of administration.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human and humanized antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible.

25           The invention provides for any method of administering lower doses of known agents (*e.g.*, appetite stimulants) than previously thought to be useful for the prevention or treatment of disease-related wasting.

#### 4.7    KITS

30           The invention provides a pharmaceutical pack or kit comprising one or more containers containing a JNK Inhibitor and optionally one or more other prophylactic or therapeutic agents useful for the treatment of HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease, chronic infectious diseases (*e.g.*, osteoarthritis and bacterial endocarditis), chronic inflammatory diseases (*e.g.*, scleroderma and mixed connective tissue disease) or tuberculosis. The invention also provides a pharmaceutical pack or kit comprising one or more containers containing one or more of the ingredients of the pharmaceutical compositions. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which

5 notice reflects approval by the agency of manufacture, use or sale for human administration; or instructions for the composition's use.

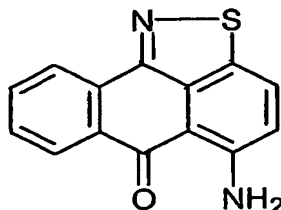
The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises a JNK Inhibitor, in one or more containers, and optionally one or more other prophylactic or therapeutic agents useful for the treatment of  
10 HIV, AIDS, cancer, end-stage renal disease, kidney failure, chronic heart disease, obstructive pulmonary disease, chronic infectious diseases (*e.g.*, osteoarthritis and bacterial endocarditis), chronic inflammatory diseases (*e.g.*, scleroderma and mixed connective tissue disease) or tuberculosis, in one or more containers.

## 5. JNK INHIBITOR ACTIVITY ASSAYS

15 The ability of a JNK Inhibitor to inhibit JNK and accordingly, to be useful for the treatment or prevention of disease-related wasting, can be demonstrated using one or more of the following assays.

### 5.1 EXAMPLE: BIOLOGICAL ACTIVITY OF 5-AMINO-ANTHRA(9,1-*CD*)ISOTHIAZOL-6-ONE

20



#### JNK Assay

To 10  $\mu$ L of 5-amino-anthra(9,1-*cd*)isothiazol-6-one in 20% DMSO/80% dilution buffer containing of 20 mM HEPES (pH 7.6), 0.1 mM EDTA, 2.5 mM magnesium chloride, 0.004% Triton x100, 2  $\mu$ g/mL leupeptin, 20 mM  $\beta$ -glycerolphosphate, 0.1 mM  
25 sodium vanadate, and 2 mM DTT in water was added 30  $\mu$ L of 50-200 ng His6-JNK1, JNK2, or JNK3 in the same dilution buffer. The mixture was pre-incubated for 30 minutes at room temperature. Sixty microliter of 10  $\mu$ g GST-c-Jun(1-79) in assay buffer consisting of 20 mM HEPES (pH 7.6), 50 mM sodium chloride, 0.1 mM EDTA, 24 mM magnesium chloride, 1 mM DTT, 25 mM PNPP, 0.05% Triton x100, 11  $\mu$ M ATP, and 0.5  $\mu$ Ci  $\gamma$ -32P  
30 ATP in water was added and the reaction was allowed to proceed for 1 hour at room temperature. The c-Jun phosphorylation was terminated by addition of 150  $\mu$ L of 12.5% trichloroacetic acid. After 30 minutes, the precipitate was harvested onto a filter plate, diluted with 50  $\mu$ L of the scintillation fluid and quantified by a counter. The IC<sub>50</sub> values

5 were calculated as the concentration of 5-amino-anthra(9,1-*cd*)isothiazol-6-one at which the c-Jun phosphorylation was reduced to 50% of the control value. Compounds that inhibit JNK preferably have an IC<sub>50</sub> value ranging 0.01 - 10  $\mu$ M in this assay. 5-Amino-anthra(9,1-*cd*)isothiazol-6-one has an IC<sub>50</sub> according to this assay of 1  $\mu$ M for JNK2 and 400 nM for JNK3. The measured IC<sub>50</sub> value for 5-amino-anthra(9,1-*cd*)isothiazol-6-one, as  
10 measured by the above assay, however, shows some variability due to the limited solubility of 5-amino-anthra(9,1-*cd*)isothiazol-6-one in aqueous media. Despite the variability, however, the assay consistently does show that 5-amino-anthra(9,1-*cd*)isothiazol-6-one inhibits JNK. This assay demonstrates that 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, inhibits JNK2 and JNK3 and, accordingly, is useful for treating  
15 or preventing disease-related wasting.

#### Selectivity For JNK:

5-Amino-anthra(9,1-*cd*)isothiazol-6-one was also assayed for its inhibitory activity against several protein kinases, listed below, using techniques known to those  
20 skilled in art (*See, e.g.*, Protein Phosphorylation, Sefton & Hunter, Eds., Academic Press, pp. 97-367, 1998). The following IC<sub>50</sub> values were obtained:

<u>Enzyme</u>	<u>IC<sub>50</sub></u>
p38-2	>30,000 nM
MEK6	>30,000 nM
25 LKK1	>30,000nM
IKK2	>30,000nM

This assay shows that 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, selectively inhibits JNK relative to other protein kinases and, accordingly, is  
30 a selective JNK Inhibitor. Therefore, 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, is useful for selectively treating or preventing disease-related wasting.

#### Jurkat T-cell IL-2 Production Assay:

35 Jurkat T cells (clone E6- 1) were purchased from the American Type Culture Collection of Manassas, VA and maintained in growth media consisting of RPMI 1640 medium containing 2 mM L-glutamine (commercially available from Mediatech Inc. of Herndon, VA), with 10% fetal bovine serum (commercially available from Hyclone Laboratories Inc. of Omaha, NE) and penicillin/streptomycin. All cells were cultured at  
40 37°C in 95% air and 5% CO<sub>2</sub>. Cells were plated at a density of 0.2 x 10<sup>6</sup> cells per well in

5 200  $\mu$ L of media. Compound stock (20 mM) was diluted in growth media and added to each well as a 10x concentrated solution in a volume of 25  $\mu$ L, mixed, and allowed to pre-incubate with cells for 30 minutes. The compound vehicle (dimethylsulfoxide) was maintained at a final concentration of 0.5% in all samples. After 30 minutes the cells were activated with PMA (phorbol myristate acetate, final concentration 50 ng/mL) and PHA  
10 (phytohemagglutinin, final concentration 2  $\mu$ g/mL). PMA and PHA were added as a 10x concentrated solution made up in growth media and added in a volume of 25  $\mu$ L per well. Cell plates were cultured for 10 hours. Cells were pelleted by centrifugation and the media removed and stored at -20°C. Media aliquots are analyzed by sandwich ELISA for the presence of IL-2 as per the manufacturers instructions (Endogen Inc. of Woburn, MA). The  
15 IC<sub>50</sub> values were calculated as the concentration of 5-amino-anthra(9,1-*cd*)isothiazol-6-one at which the IL-2 production was reduced to 50% of the control value. Compounds that inhibit JNK preferably have an IC<sub>50</sub> value ranging from 0.1 - 30  $\mu$ M in this assay. 5-Amino-anthra(9,1-*cd*)isothiazol-6-one has an IC<sub>50</sub> of 30  $\mu$ M. The measured IC<sub>50</sub> value for 5-amino-anthra(9,1-*cd*)isothiazol-6-one, as measured by the above assay, however, shows some  
20 variability due to the limited solubility of 5-amino-anthra(9,1-*cd*)isothiazol-6-one in aqueous media. Despite the variability, however, the assay consistently does show that 5-amino-anthra(9,1-*cd*)isothiazol-6-one inhibits JNK.

This assay shows that 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, inhibits IL-2 production in Jurkat T-cells and accordingly inhibits JNK.  
25 Therefore, 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, is useful for treating or preventing disease-related wasting.

#### [<sup>3</sup>H]Dopamine Cell Culture Assay:

Cultures of dopaminergic neurons were prepared according to a modification  
30 of the procedure described by Raymon and Leslie (*J. Neurochem.* 62:1015-1024, 1994). Time-mated pregnant rats were sacrificed on embryonic day 14 - 15 (crown rump length 11 - 12 mm) and the embryos removed by cesarean section. The ventral mesencephalon, containing the dopaminergic neurons, was dissected from each embryo. Tissue pieces from approximately 48 embryos were pooled and dissociated both enzymatically and  
35 mechanically. An aliquot from the resulting cell suspension was counted and the cells were plated in high glucose DMEM/F12 culture medium with 10% fetal bovine serum at a density of  $1 \times 10^5$  cells/well of a Biocoat poly-D-lysine-coated 96-well plate. The day following plating was considered 1 day *in vitro* (DIV). Cells were maintained in a stable environment at 37°C, 95% humidity, and 5% CO<sub>2</sub>. A partial medium change was

5 performed at 3 DIV. At 7 DIV, cells were treated with the neurotoxin, 6-hydroxydopamine (6-OHDA, 30  $\mu$ M) in the presence and absence of 5-amino-anthra(9,1-*cd*)isothiazol-6-one. Cultures were processed for [ $^3$ H]dopamine uptake 22 hours later.

[ $^3$ H]Dopamine uptake is used as a measure of the health and integrity of dopaminergic neurons in culture (Prochiantz et al., *PNAS* 76: 5387-5391, 1979). It was used in these studies to monitor the viability of dopaminergic neurons following exposure to the neurotoxin 6-OHDA. 6-OHDA has been shown to damage dopaminergic neurons both *in vitro* and *in vivo* and is used to model the cell death observed in Parkinson's disease (Ungerstedt, U., *Eur. J. Pharm.*, 5 (1968) 107-110 and Hefti et al., *Brain Res.*, 195 (1980) 123-137). Briefly, cells treated with 6-OHDA in the presence and absence of 5-amino-anthra(9,1-*cd*)isothiazol-6-one were assessed in the uptake assay 22 hrs after exposure to 6-OHDA. Culture medium was removed and replaced with warm phosphate buffered saline (PBS) with calcium and magnesium, 10  $\mu$ M pargyline, 1 mM ascorbic acid, and 50 nM [ $^3$ H]dopamine. Cultures were incubated at 37°C for 20 min. Radioactivity was removed and the cultures were washed 3x with ice cold PBS. To determine the intracellular accumulation of [ $^3$ H]dopamine, cells were lysed with M-PER detergent and an aliquot was taken for liquid scintillation counting. The measured effect of 5-amino-anthra(9,1-*cd*)isothiazol-6-one on the intracellular accumulation of [ $^3$ H]dopamine, as measured by the above assay, however, shows some variability due to the limited solubility of 5-amino-anthra(9,1-*cd*)isothiazol-6-one in aqueous media. Despite the variability, however, the assay consistently does show that 5-amino-anthra(9,1-*cd*)isothiazol-6-one protects rat ventral mesencephalan neurons from the toxic effects of 6-OHDA. Accordingly, 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, is useful for treating or preventing disease-related wasting.

#### 30 Brain-Blood Plasma Distribution of 5-amino-anthra(9,1-*cd*)isothiazol-6-one *In Vivo*

5-Amino-anthra(9,1-*cd*)isothiazol-6-one was administered intravenously (10 mg/kg) into the veins of Sprague-Dawley rats. After 2 hr, blood samples were obtained from the animals and their vascular systems were perfused with approximately 100 mL of saline to rid their brains of blood. The brains were removed from the animals, weighed, and homogenized in a 50 mL conical tube containing 10 equivalents (w/v) of methanol/saline (1:1) using a Tissue Tearer (Fischer Scientific). The homogenized material was extracted by adding 600  $\mu$ L of cold methanol to 250  $\mu$ L of brain homogenate vortexed for 30 sec and subjected to centrifugation for 5 min. After centrifugation, 600  $\mu$ L of the resulting supernatant was transferred to a clean tube and evaporated at room temperature under

5 reduced pressure to provide a pellet. The resulting pellet was reconstituted in 250  $\mu$ L of 30% aqueous methanol to provide a brain homogenate analysis sample. A plasma analysis sample was obtained using the brain homogenate analysis sample procedure described above by substituting plasma for brain homogenate. Standard plasma samples and standard brain homogenate samples containing known amounts of 5-amino-anthra(9,1-*cd*)isothiazol-10 6-one were also prepared by adding 5  $\mu$ L of serial dilutions (50:1) of a solution of 5-amino-anthra(9,1-*cd*)isothiazol-6-one freshly prepared in cold ethanol to 250  $\mu$ L of control rat plasma (Bioreclamation of Hicksville, NY) or control brain homogenate. The standard plasma samples and standard brain homogenate samples were then subjected to the same extraction by protein precipitation, centrifugation, evaporation, and reconstitution procedure 15 used for the brain homogenate to provide brain homogenate standard analysis samples and plasma standard analysis samples. The brain homogenate analysis samples, plasma analysis samples, and standard analysis samples were analyzed and compared using HPLC by injecting 100  $\mu$ L of a sample onto a 5  $\mu$ m C-18 Luna column (4.6 mm x 150 mm, commercially available from Phenomenex of Torrance, CA) and eluting at 1 mL/min with a 20 linear gradient of 30% aqueous acetonitrile containing 0.1% trifluoroacetic acid to 90% aqueous acetonitrile containing 0.1% trifluoroacetic acid over 8 minutes and holding at 90% aqueous acetonitrile containing 0.1% trifluoroacetic acid for 3 min. with absorbance detection at 450 nm. Recovery of 5-amino-anthra(9,1-*cd*)isothiazol-6-one was  $56 \pm 5.7\%$  for plasma and  $42 \pm 6.2\%$  for the brain. The concentration of 5-amino-anthra(9,1-*cd*) 25 isothiazol-6-one in the brain and plasma was determined by comparing HPLC chromatograms obtained from the brain homogenate analysis samples and plasma analysis samples to standard curves constructed from analysis of the brain homogenate standard analysis samples and the plasma standard analysis samples, respectively. Results from this study show that 5-amino-anthra(9,1-*cd*)isothiazol-6-one, following intravenous 30 administration, crosses the blood-brain barrier to a significant extent. In particular, brain-drug concentrations were approximately 65 nmole/g and plasma concentrations were approximately 7  $\mu$ M at 2 hr post-dose, resulting in a brain-plasma concentration ratio of approximately 9-fold (assuming 1 g of brain tissue is equivalent to 1 mL of plasma). This example shows that 5-amino-anthra(9,1-*cd*)isothiazol-6-one, an illustrative JNK Inhibitor, 35 has enhanced ability to cross the blood-brain barrier. In addition, this example shows that the JNK Inhibitors, in particular 5-amino-anthra(9,1-*cd*)isothiazol-6-one, can cross the blood-brain barrier when administered to a patient.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, the invention described and claimed

- 5 herein is not to be limited in scope by the specific embodiments herein disclosed. These  
embodiments are intended as illustrations of several aspects of the invention. Any  
equivalent embodiments are intended to be within the scope of this invention. Indeed,  
various modifications of the invention in addition to those shown and described herein will  
become apparent to those skilled in the art from the foregoing description. Such  
10 modifications are also intended to fall within the scope of the appended claims.

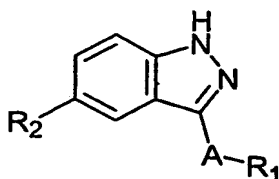
A number of references have been cited, the entire disclosure of which are  
incorporated herein by reference in their entirety.

5 What is claimed is:

1. A method for treating disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor.

2. A method for preventing disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor.

10 3. A method for treating or preventing disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a compound having the following formula:



15 or a pharmaceutically acceptable salt thereof,

wherein:

A is a direct bond,  $-(CH_2)_a-$ ,  $-(CH_2)_bCH=CH(CH_2)_c-$ , or  $-(CH_2)_bC\equiv C(CH_2)_c-$ ;

R<sub>1</sub> is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R<sub>3</sub>;

20 R<sub>2</sub> is -R<sub>3</sub>, -R<sub>4</sub>,  $-(CH_2)_bC(=O)R_5$ ,  $-(CH_2)_bC(=O)OR_5$ ,  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)NR_6R_7$ ,  $-(CH_2)_bNR_5R_6$ ,  $-(CH_2)_bOR_5$ ,  $-(CH_2)_bSO_dR_5$  or  $-(CH_2)_bSO_2NR_5R_6$ ;

a is 1, 2, 3, 4, 5 or 6;

25 b and c are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

d is at each occurrence 0, 1 or 2;

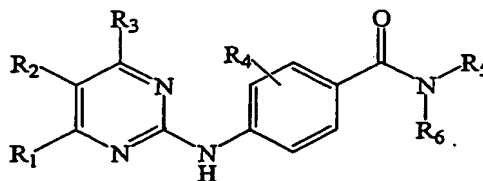
R<sub>3</sub> is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, heterocycle, heterocycloalkyl,  $-C(=O)OR_8$ ,  $-OC(=O)R_8$ ,  $-C(=O)NR_8R_9$ , -

- 5 C(=O)NR<sub>8</sub>OR<sub>9</sub>, -SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, -CN, -NO<sub>2</sub>, -NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>C(=O)R<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>OR<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>R<sub>9</sub>, -O(CH<sub>2</sub>)<sub>b</sub>NR<sub>8</sub>R<sub>9</sub>, or heterocycle fused to phenyl;

R<sub>4</sub> is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R<sub>3</sub>, or R<sub>4</sub> is halogen or hydroxy;

- 10 R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are optionally substituted with one to four substituents independently selected from R<sub>3</sub>; and R<sub>8</sub> and R<sub>9</sub> are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R<sub>8</sub> and R<sub>9</sub> taken together with the atom or
- 15 atoms to which they are bonded form a heterocycle, wherein each of R<sub>8</sub>, R<sub>9</sub>, and R<sub>8</sub> and R<sub>9</sub> taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R<sub>3</sub>.

4. A method for treating or preventing disease-related wasting in a patient, comprising
- 20 administering to a patient in need thereof an effective amount of a compound having the following formula:



- 25 or a pharmaceutically acceptable salt thereof,

wherein:

R<sub>1</sub> is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R<sub>7</sub>;

R<sub>2</sub> is hydrogen;

- 30 R<sub>3</sub> is hydrogen or lower alkyl;

R<sub>4</sub> represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

- 5  $R_5$  and  $R_6$  are the same or different and independently  $-R_8$ ,  $-(CH_2)_aC(=O)R_9$ ,  $-(CH_2)_aC(=O)OR_9$ ,  $-(CH_2)_aC(=O)NR_9R_{10}$ ,  $-(CH_2)_aC(=O)NR_9(CH_2)_bC(=O)R_{10}$ ,  $-(CH_2)_aNR_9C(=O)R_{10}$ ,  $(CH_2)_aNR_{11}C(=O)NR_9R_{10}$ ,  $-(CH_2)_aNR_9R_{10}$ ,  $-(CH_2)_aOR_9$ ,  $-(CH_2)_aSO_cR_9$  or  $-(CH_2)_aSO_2NR_9R_{10}$ ;

- 10 or  $R_5$  and  $R_6$  taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

- $R_7$  is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl,  $-C(=O)OR_8$ ,  $-OC(=O)R_8$ ,  $-C(=O)NR_8R_9$ ,  $-C(=O)NR_8OR_9$ ,  $-SO_cR_8$ ,  $-SO_cNR_8R_9$ ,  $-NR_8SO_cR_9$ ,  $-NR_8R_9$ ,  $-NR_8C(=O)R_9$ ,  $-NR_8C(=O)(CH_2)_bOR_9$ ,  $-NR_8C(=O)(CH_2)_bR_9$ ,  $-O(CH_2)_bNR_8R_9$ , or heterocycle fused to phenyl;
- 15

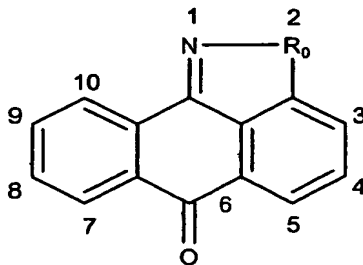
$R_8$ ,  $R_9$ ,  $R_{10}$  and  $R_{11}$  are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl;

- 20 or  $R_8$  and  $R_9$  taken together with the atom or atoms to which they are attached to form a heterocycle;

$a$  and  $b$  are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

$c$  is at each occurrence 0, 1 or 2.

- 25 5. A method for treating or preventing disease-related wasting in a patient, comprising administering to a patient in need thereof an effective amount of a compound having the following formula:

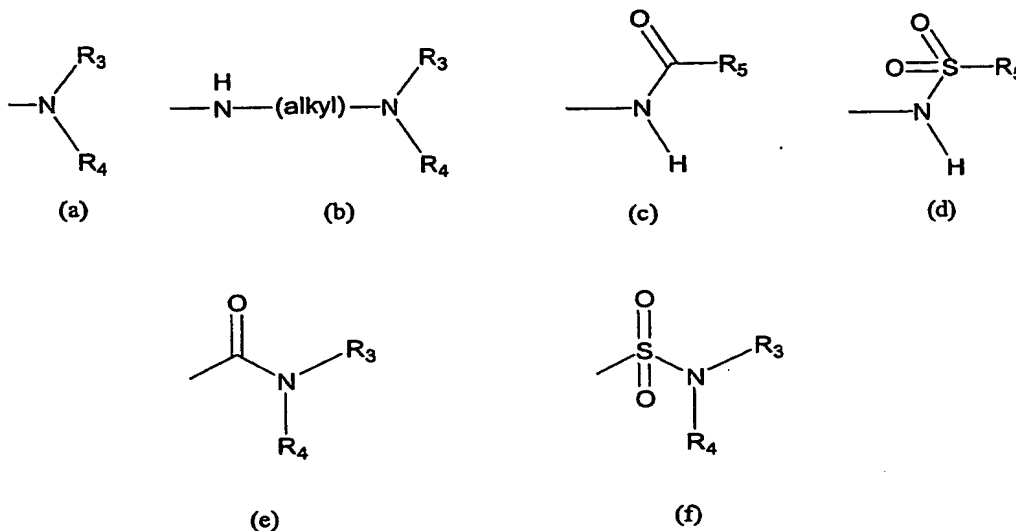


- 30 or a pharmaceutically acceptable salt thereof,

5 wherein  $R_0$  is -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, NH or -CH<sub>2</sub>-;

the compound being (i) unsubstituted, (ii) monosubstituted and having a first substituent, or (iii) disubstituted and having a first substituent and a second substituent;

10 the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position, wherein the first and second substituent, when present, are independently alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by



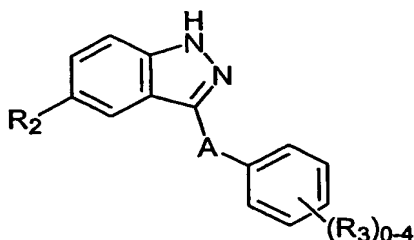
formula (a), (b), (c), (d), (e), or (f):

15 wherein  $R_3$  and  $R_4$  are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or  $R_3$  and  $R_4$  are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

20  $R_5$  is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxycarbonylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

6. The method of claim 3 wherein A is a direct bond.

- 5 7. The method of claim 3 wherein A is  $-(CH_2)_a-$ .
8. The method of claim 3 wherein A is  $-(CH_2)_bCH=CH(CH_2)_c-$ .
9. The method of claim 3 wherein A is  $-(CH_2)_bC \equiv C(CH_2)_c-$ .
10. The method of claim 3 wherein the compound has the following formula:



10

or a pharmaceutically acceptable salt thereof,

wherein:

A is a direct bond,  $-(CH_2)_a-$ ,  $-(CH_2)_bCH=CH(CH_2)_c-$ , or  $-(CH_2)_bC \equiv C(CH_2)_c-$ ;

- 15  $R_1$  is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ ;

$R_2$  is  $-R_3$ ,  $-R_4$ ,  $-(CH_2)_bC(=O)R_5$ ,  $-(CH_2)_bC(=O)OR_5$ ,  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)NR_6R_7$ ,  $-(CH_2)_bNR_5R_6$ ,  $-(CH_2)_bOR_5$ ,  $-(CH_2)_bSO_dR_5$  or  $-(CH_2)_bSO_2NR_5R_6$ ;

$a$  is 1, 2, 3, 4, 5 or 6;

- 20  $b$  and  $c$  are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

$d$  is at each occurrence 0, 1 or 2;

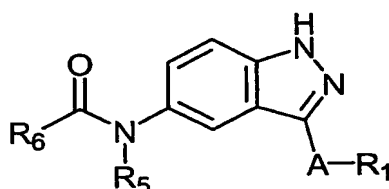
- 25  $R_3$  is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl,  $-C(=O)OR_8$ ,  $-OC(=O)R_8$ ,  $-C(=O)NR_8R_9$ ,  $-C(=O)NR_8OR_9$ ,  $-SO_2NR_8R_9$ ,  $-NR_8SO_2R_9$ ,  $-CN$ ,  $-NO_2$ ,  $-NR_8R_9$ ,  $-NR_8C(=O)R_9$ ,  $-NR_8C(=O)(CH_2)_bOR_9$ ,  $-NR_8C(=O)(CH_2)_bR_9$ ,  $-O(CH_2)_bNR_8R_9$ , or heterocycle fused to phenyl;

5  $R_4$  is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ , or  $R_4$  is halogen or hydroxy;

$R_5$ ,  $R_6$  and  $R_7$  are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of  $R_5$ ,  $R_6$  and  $R_7$  are optionally substituted with one to four substituents independently selected from  $R_3$ ; and

10  $R_8$  and  $R_9$  are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or  $R_8$  and  $R_9$  taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of  $R_8$ ,  $R_9$ , and  $R_8$  and  $R_9$  taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from  $R_3$ .

15 11. The method of claim 3 wherein the compound has the following formula:



20 or a pharmaceutically acceptable salt thereof,

wherein:

A is a direct bond,  $-(CH_2)_a-$ ,  $-(CH_2)_bCH=CH(CH_2)_c-$ , or  $-(CH_2)_bC \equiv C(CH_2)_c-$ ;

$R_1$  is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ ;

25  $R_2$  is  $-R_3$ ,  $-R_4$ ,  $-(CH_2)_bC(=O)R_5$ ,  $-(CH_2)_bC(=O)OR_5$ ,  $-(CH_2)_bC(=O)NR_5R_6$ ,  $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)R_6$ ,  $-(CH_2)_bNR_5C(=O)NR_6R_7$ ,  $-(CH_2)_bNR_5R_6$ ,  $-(CH_2)_bOR_5$ ,  $-(CH_2)_bSO_dR_5$  or  $-(CH_2)_bSO_2NR_5R_6$ ;

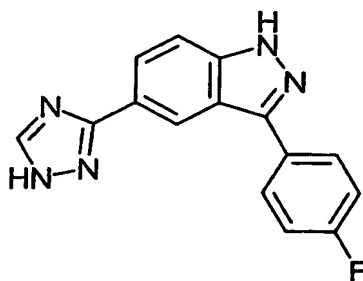
$a$  is 1, 2, 3, 4, 5 or 6;

$b$  and  $c$  are the same or different and at each occurrence independently selected from 0, 1, 2,

30 3 or 4;

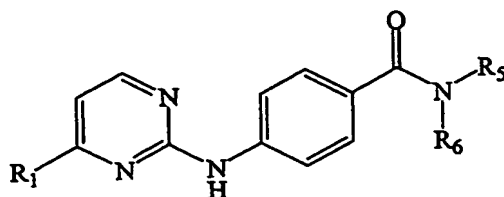
$d$  is at each occurrence 0, 1 or 2;

- 5  $R_3$  is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl,  $-C(=O)OR_8$ ,  $-OC(=O)R_8$ ,  $-C(=O)NR_8R_9$ ,  $-C(=O)NR_8OR_9$ ,  $-SO_2NR_8R_9$ ,  $-NR_8SO_2R_9$ ,  $-CN$ ,  $-NO_2$ ,  $-NR_8R_9$ ,  $-NR_8C(=O)R_9$ ,  $-NR_8C(=O)(CH_2)_bOR_9$ ,  $-NR_8C(=O)(CH_2)_bR_9$ ,  $-O(CH_2)_bNR_8R_9$ , or heterocycle fused to phenyl;
- 10  $R_4$  is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from  $R_3$ , or  $R_4$  is halogen or hydroxy;
- $R_5$ ,  $R_6$  and  $R_7$  are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of  $R_5$ ,  $R_6$  and  $R_7$  are optionally substituted with one to four substituents independently selected from  $R_3$ ; and
- 15  $R_8$  and  $R_9$  are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or  $R_8$  and  $R_9$  taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of  $R_8$ ,  $R_9$ , and  $R_8$  and  $R_9$  taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from  $R_3$ .
- 20 12. The method of claim 3 wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof.

- 5 13. The method of claim 4, wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof,

wherein:

- 10 R<sub>1</sub> is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R<sub>7</sub>;

R<sub>2</sub> is hydrogen;

R<sub>3</sub> is hydrogen or lower alkyl;

- 15 R<sub>4</sub> represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

R<sub>5</sub> and R<sub>6</sub> are the same or different and independently -R<sub>8</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)R<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>(CH<sub>2</sub>)<sub>b</sub>C(=O)R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>C(=O)R<sub>10</sub>, (CH<sub>2</sub>)<sub>a</sub>NR<sub>11</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>SO<sub>2</sub>R<sub>9</sub> or -(CH<sub>2</sub>)<sub>a</sub>SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>;

- 20 or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

- R<sub>7</sub> is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(=O)OR<sub>8</sub>, -OC(=O)R<sub>8</sub>, -C(=O)NR<sub>8</sub>R<sub>9</sub>, -C(=O)NR<sub>8</sub>OR<sub>9</sub>, -SO<sub>2</sub>R<sub>8</sub>, -SO<sub>2</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>SO<sub>2</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>C(=O)R<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>OR<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>R<sub>9</sub>, -O(CH<sub>2</sub>)<sub>b</sub>NR<sub>8</sub>R<sub>9</sub>, or heterocycle fused to phenyl;
- 25

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, heterocycle,

- 30 heterocycloalkyl;

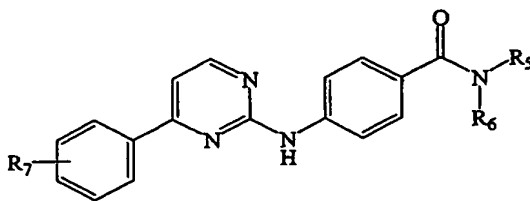
5 or R<sub>8</sub> and R<sub>9</sub> taken together with the atom or atoms to which they are attached to form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

10

14. The method of claim 4, wherein the compound has the following formula:



15 or a pharmaceutically acceptable salt thereof,

wherein:

R<sub>1</sub> is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R<sub>7</sub>;

R<sub>2</sub> is hydrogen;

20 R<sub>3</sub> is hydrogen or lower alkyl;

R<sub>4</sub> represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

R<sub>5</sub> and R<sub>6</sub> are the same or different and independently -R<sub>8</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)R<sub>9</sub>, -  
 (CH<sub>2</sub>)<sub>a</sub>C(=O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>(CH<sub>2</sub>)<sub>b</sub>C(=O)R<sub>10</sub>, -  
 25 (CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>C(=O)R<sub>10</sub>, (CH<sub>2</sub>)<sub>a</sub>NR<sub>11</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>OR<sub>9</sub>, -  
 (CH<sub>2</sub>)<sub>a</sub>SO<sub>c</sub>R<sub>9</sub> or -(CH<sub>2</sub>)<sub>a</sub>SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>;

or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

R<sub>7</sub> is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl,  
 30 alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl,  
 arylalkyl, heterocycle, heterocycloalkyl, -C(=O)OR<sub>8</sub>, -OC(=O)R<sub>8</sub>, -C(=O)NR<sub>8</sub>R<sub>9</sub>, -

- 5 C(=O)NR<sub>8</sub>OR<sub>9</sub>, -SO<sub>c</sub>R<sub>8</sub>, -SO<sub>c</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>SO<sub>c</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>C(=O)R<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>OR<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>R<sub>9</sub>, -O(CH<sub>2</sub>)<sub>b</sub>NR<sub>8</sub>R<sub>9</sub>, or heterocycle fused to phenyl;

R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;

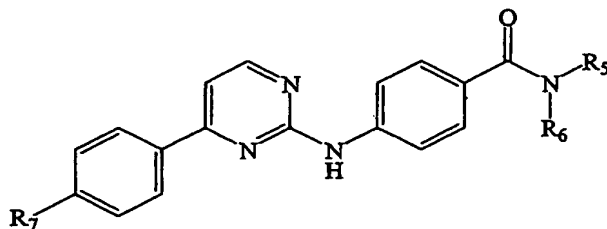
- 10 or R<sub>8</sub> and R<sub>9</sub> taken together with the atom or atoms to which they are attached to form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

15

15. The method of claim 4, wherein the compound has the following formula:



- 20 or a pharmaceutically acceptable salt thereof,

wherein:

R<sub>1</sub> is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R<sub>7</sub>;

R<sub>2</sub> is hydrogen;

- 25 R<sub>3</sub> is hydrogen or lower alkyl;

R<sub>4</sub> represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

R<sub>5</sub> and R<sub>6</sub> are the same or different and independently -R<sub>8</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)R<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)OR<sub>9</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>C(=O)NR<sub>9</sub>(CH<sub>2</sub>)<sub>b</sub>C(=O)R<sub>10</sub>, -

- 5 (CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>C(=O)R<sub>10</sub>, (CH<sub>2</sub>)<sub>a</sub>NR<sub>11</sub>C(=O)NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>NR<sub>9</sub>R<sub>10</sub>, -(CH<sub>2</sub>)<sub>a</sub>OR<sub>9</sub>, -  
(CH<sub>2</sub>)<sub>a</sub>SO<sub>c</sub>R<sub>9</sub> or -(CH<sub>2</sub>)<sub>a</sub>SO<sub>2</sub>NR<sub>9</sub>R<sub>10</sub>;

or R<sub>5</sub> and R<sub>6</sub> taken together with the nitrogen atom to which they are attached to form a heterocycle;

- 10 R<sub>7</sub> is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(=O)OR<sub>8</sub>, -OC(=O)R<sub>8</sub>, -C(=O)NR<sub>8</sub>R<sub>9</sub>, -  
C(=O)NR<sub>8</sub>OR<sub>9</sub>, -SO<sub>c</sub>R<sub>8</sub>, -SO<sub>c</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>SO<sub>c</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>C(=O)R<sub>9</sub>, -  
NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>OR<sub>9</sub>, -NR<sub>8</sub>C(=O)(CH<sub>2</sub>)<sub>b</sub>R<sub>9</sub>, -O(CH<sub>2</sub>)<sub>b</sub>NR<sub>8</sub>R<sub>9</sub>, or heterocycle fused to phenyl;

- 15 R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub> and R<sub>11</sub> are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;

or R<sub>8</sub> and R<sub>9</sub> taken together with the atom or atoms to which they are attached to form a heterocycle;

- 20 *a* and *b* are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

*c* is at each occurrence 0, 1 or 2.

16. The method of claim 5, wherein R<sub>0</sub> is -O-.

25 17. The method of claim 5, wherein R<sub>0</sub> is -S-.

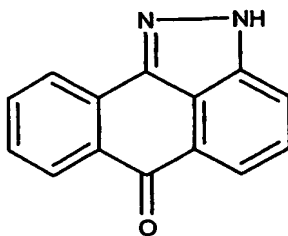
18. The method of claim 5, wherein R<sub>0</sub> is -S(O)-.

30 19. The method of claim 5, wherein R<sub>0</sub> is -S(O)<sub>2</sub>-.

20. The method of claim 5, wherein R<sub>0</sub> is NH.

21. The method of claim 5, wherein R<sub>0</sub> is CH<sub>2</sub>-.

- 5 22. The method of claim 5, wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof.

- 10 23. The method of claim 1 further comprising administering a prophylactic or therapeutic agent.
24. The method of claim 2 further comprising administering a prophylactic or therapeutic agent.
25. The method of claim 3 further comprising administering a prophylactic or  
15 therapeutic agent.
26. The method of claim 5 further comprising administering a prophylactic or therapeutic agent.
27. The method of claim 5 further comprising administering a prophylactic or therapeutic agent.
- 20 28. The method of claim 1, wherein the disease is HIV, AIDS, end-stage renal disease, kidney failure, cancer, tuberculosis, chronic heart failure, chronic pulmonary disease, rheumatoid arthritis, scleroderma, mixed connective tissue disease, osteoarthritis or bacterial endocarditis.
- 25 29. The method of claim 2, wherein the disease is HIV, AIDS, end-stage renal disease, kidney failure, cancer, tuberculosis, chronic heart failure, chronic pulmonary disease, rheumatoid arthritis, scleroderma, mixed connective tissue disease, osteoarthritis or bacterial endocarditis.
- 30 30. The method of claim 3, wherein the disease is HIV, AIDS, end-stage renal disease, kidney failure, cancer, tuberculosis, chronic heart failure, chronic pulmonary disease, rheumatoid arthritis, scleroderma, mixed connective tissue disease, osteoarthritis or bacterial endocarditis.

- 5 31. The method of claim 4, wherein the disease is HIV, AIDS, end-stage renal disease, kidney failure, cancer, tuberculosis, chronic heart failure, chronic pulmonary disease, rheumatoid arthritis, scleroderma, mixed connective tissue disease, osteoarthritis or bacterial endocarditis.
- 10 32. The method of claim 5, wherein the disease is HIV, AIDS, end-stage renal disease, kidney failure, cancer, tuberculosis, chronic heart failure, chronic pulmonary disease, rheumatoid arthritis, scleroderma, mixed connective tissue disease, osteoarthritis or bacterial endocarditis.